

# Health economic aspects of low back pain

Gylfi Ólafsson



**Karolinska  
Institutet**

From Department of Learning, Informatics, Management and Ethics,  
Medical Management Centre,  
Karolinska Institutet, Stockholm, Sweden

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# Health economic aspects of low back pain

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

**Gylfi Ólafsson**

*Principal Supervisor:*

Fredrik Borgström  
Karolinska Institutet  
Department of LIME

*Co-supervisors:*

Peter Fritzell  
Futurum Academy, Jönköping

Tinna Laufey Ásgeirsdóttir  
University of Iceland  
Department of Economics

*Opponent:*

Johan Jarl  
Lund University  
Department of Clinical Sciences  
Faculty of medicine

*Examination Board:*

Jan Hartvigsen  
Syddansk Universitet  
Department of Sports Science and Clinical  
Biomechanics

Lars-Åke Levin  
Linköping University  
Department of Medical and Health Sciences  
Division of Health Care Analysis

Anders Wimo  
Karolinska Institutet  
Department of Neurobiology, Care Sciences and  
Society  
Division of Neurogeriatrics



## ABSTRACT

Four out of five people experience low back pain sometime during their lifetime. Problems of the back—and to a less extent of the neck—are consistently in the top seats among the most burdensome diseases in the developed world. In addition to its often-debilitating pain, low back pain is a major contributor to health care costs and lost productivity. Health economics is the study of how the health care system's scarce resources can and should be used to maximise health.

The objective of this thesis is to enhance the understanding of the economic aspects of low back pain. The overarching research themes are two. First, are surgical interventions for low back pain cost-effective? Second, what is its burden in Sweden?

The first two papers present results from analyses of a vast database assembled from a range of Swedish institutions covering health care consumption of all patients with low back pain in the Västra Götaland region during 2000–2012. The former paper shows that the national cost of all patients that experienced an episode of low back pain in 2011 was €739 million or €78 per capita. Of this, 65% were due to indirect costs such as absence from work.

The second paper draws on the dataset to create an economic model. It shows that although the majority of patients improve within a few months at a relatively low cost, the sheer number of patients experiencing back pain make the disease costly.

Narrowing down, using results from a randomised controlled trial, the third paper shows that under certain assumptions, surgical treatment of degenerative disc disease is cost-effective when compared to multidisciplinary treatment involving physical therapy and cognitive behavioural therapy. The results are not robust to different assumptions and the interpretation of the results should take that into account.

The fourth and last paper also uses results from a randomised controlled trial of decompression surgery for spinal stenosis. This type of surgery, the most common of all spinal surgeries, involves treating the spinal stenosis—painful narrowing of the spinal canal—with decompression, where parts of bone and soft tissue are removed to make room for the nerves. The study shows with robust results that fusing vertebra together as part of decompression surgery increases costs with neither short-term nor long-term benefits.

This dissertation shows that the burden of low back pain, including lumbar spinal stenosis and lumbar disc herniation, is not only heavy but distributed widely within and outside of the health care system. Although most treatments are effective, this thesis shows an example of treatments that are being used extensively but are in fact quite wasteful. This could not have been shown without careful research and robust methodology. In order to improve the use of money within the health care, research needs to be conducted to assess where to spend it.

## LIST OF SCIENTIFIC PAPERS

- I. Olafsson G., Jonsson E., Fritzell P., Hägg O., Borgström [2018] Cost of low back pain: results from a national register study in Sweden. Submitted to European Spine Journal.
- II. Olafsson, G., Jonsson, E., Fritzell, P., Hägg, O., & Borgström, F. (2017). A health economic lifetime treatment pathway model for low back pain in Sweden. *Journal of Medical Economics*, 20(12), 1281–1289. DOI:10.1080/13696998.2017.1372252
- III. Johnsen, L. G., Hellum, C., Storheim, K., Nygaard, Ø. P., Brox, J. I., Rossvoll, I., ... Fritzell, P. (2014). Cost-Effectiveness of Total Disc Replacement Versus Multidisciplinary Rehabilitation in Patients With Chronic Low Back Pain. *Spine*, 39(1), 23–32. DOI: 10.1097/BRS.0000000000000065
- IV. Försth, P., Ólafsson, G., Carlsson, T., Frost, A., Borgström, F., Fritzell, P., ... Sandén, B. (2016). A Randomized, Controlled Trial of Fusion Surgery for Lumbar Spinal Stenosis. *The New England Journal of Medicine*, 374(15), 1413–1423. DOI: 10.1056/NEJMoa1513721

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## LIST OF ABBREVIATIONS

ATC	Anatomic therapeutic classification (of pharmaceuticals)
CBT	Cognitive behavioural therapy
CE	Cost effectiveness
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
D	Decompression surgery
D+F	Decompression surgery with fusion
DALY	Disability-adjusted life years
DDD	Degenerative disc disease
DS	Degenerative spondylolisthesis
GDP	Gross domestic product
GP	General practitioner
ICD	International classification of diseases
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LBP	Low back pain
LDH	Lumbar disc herniation
LSS	Lumbar spinal stenosis
MD	Markov death sub-model
MDR	Multidisciplinary rehabilitation
MNSC	Markov non-surgical care sub-model
MPSC	Markov post-surgical care sub-model
MRI	Magnetic resonance imaging
NOK	Norwegian krona
ODI	Oswestry disability index
PP	Per-protocol (analysis)
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SG	Standard gamble
TDR	Total disc replacement
TTO	Time trade-off
VGR	Västra Götaland region
WTP	Willingness to pay

# 1 INTRODUCTION

Health economics is the study of allocation of scarce resources. Moreover, it possesses a toolbox for how these resources can be used to maximise health or other desired outcomes.

Low back pain (LBP) is one of the most burdensome diseases in the developed world [1]. Its causes are wide-ranging and involve both the soft and hard tissues of the back. Diagnostics are difficult and error-prone. Treatments are similarly wide-ranging, from mild analgesics through cognitive therapy, physical therapy and surgery. The effectiveness of treatments varies and is often contested. Although improvements have been made in the last decades, treatment options and diagnostic procedures have not been shown to be universally effective [2].

The objective of this thesis is to enhance the understanding of the economic aspects of LBP. The research themes are two: What is the burden of LBP in Sweden, and what can be said about the cost-effectiveness of treatment, in particular surgical treatments.

## 2 BACKGROUND

### 2.1 LOW BACK PAIN

Pain and symptoms of the back and neck are currently the biggest burden of Western societies in terms of years lived with disability, according to studies commissioned by the World Health Organisation [3]. Low back pain (LBP) specifically has been estimated to affect 80–85% of the world's population at some point during a lifetime [4].

Prevalence of chronic LBP is rising [5]. LBP has a wide range of causes and correspondingly, treatments and outcomes vary widely. Not less important, accurate diagnosis is difficult, leading to the same conditions getting different diagnoses and subsequently different treatment. In addition to strictly referring to pain confined to the lower spine, the term LBP is also used to refer to pain and problems in the legs when these can be traced to the lower back. Symptoms often resolve within 3 months by itself, or for example after physical therapy and other non-surgical regimens.

However, for a proportion of patients, the condition becomes chronic (defined as pain limiting usual activities for at least 3 months). If symptoms persist, patients may be referred to orthopaedic or neurosurgical specialists, evaluating whether surgery is indicated [6].

The number of surgical treatments have increased dramatically, especially in the US, where the number of spinal fusions per year has increased by 55% during the last decade [7]. Although a relatively low proportion of patients need to undergo surgery, the high number of LBP cases make the total number of surgeries high.

This makes direct costs, such as to diagnosis, physical therapy, surgeries and medications high. Nevertheless, studies have shown that the direct costs are dwarfed by indirect costs, such as absence from work. In developed countries, these constitute 70–90% of the total economic cost related to LBP [8–10].

This thesis investigates detail on the treatment of two specific conditions. The former is whether to treat degenerative disc disease surgically or non-surgically. The latter is whether adding fusion to a decompression surgery for lumbar spinal stenosis is warranted. These are described shortly in turn.

Degenerative disc disease (DDD) refers to the degeneration of the spinal motion segment. Disc degeneration is associated with aging and is commonly asymptomatic. When symptomatic, however, it can cause significant and debilitating pain [11]. Non-surgical treatment is the preferred first-line treatment, including activity modification, pain medications, and physical therapy. When non-operative management fails, and the origin of the pain can be established, surgical fusion to eliminate painful motion can be indicated [11]. In recent years, total disc replacement (TDR) has been introduced as an alternative to fusion in selected patients [12]. Mean age in surgically treated DDD-patients is around 45 years.

Lumbar spinal stenosis in contrast is caused by a gradual narrowing of the spinal canal. Patients with lumbar spinal stenosis, a degenerative disorder affecting elderly with a mean age around 70 years, typically have both pain in their lower back and legs when walking. This condition severely restricts function, walking ability, and quality of life. Of all indications for spinal surgery, lumbar spinal stenosis has become the most common [13], explained by an aging population.

## 2.2 HEALTH ECONOMICS

Economics are commonly defined as the study of scarce resources. Health economics, by extension, is the study of allocation of scarce resources wherever health or healthcare are involved, usually focused on costs (inputs) and the consequences (outcomes) of health care interventions. As it incorporates elements from medicine and pharmacology, among other fields, it is not considered just as a branch of economics, but rather a related multidisciplinary field [14].

With progress in pharmacology and medicine in general, ever more treatment options are available, competing for the finite resources allocated to health care. In light of this, physicians and other decision-makers turn to health economics as scientific and sound economic evaluations of health-care interventions are critical for decision-making in health care if the goal is to optimize the life and health obtained with given resources.

Health-economic evaluations can be valuable when deciding whether the gains following a specific treatment, both in terms of health in savings within the health-care system or society at large, can be justified. Costs can in this sense be seen as not the money *per se* that an intervention requires, but rather the foregone use of the same money, whether within or outside the health-care system. The onus is on the healthcare system and health economists to make sure the available money is put to the optimal use.

Seen in relation to the incidence and high economic impact of LBP, economic evaluations of different interventions are scarce. Surgery may be considered as expensive. Patients and their relatives may lose many days of work, and the costs of rehabilitation can be considerable. The main tools and concepts of health economics as used in this thesis are presented in turn.

### 2.2.1 Quality of life and quality-adjusted life years

When allocating resources across the whole health care system, consequences of the spending can be wide-ranging. Longer life provided by one treatment might need to be compared with less pain by another, less anxiety or lower risk of an uncertain outcome. To overcome the heterogeneity of this, a one-dimensional instrument was needed to assess quality of life (QoL). By multiplying QoL by the time in which a person spends in a given state, a measure of quality-adjusted life years (QALYs) can be calculated. Using this measure, treatments with disparaging outcomes can be compared on a shared metric.

To assess QoL, several metrics have been developed. EQ-5D is the most commonly-used one available. It is a generic measure of utility that generates an index-based summary score based on societal preference weights. It includes measures of health status across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, from which a utility index score is computed that can range from less than 0 (worse than dead) to 1 (perfect health).

SF-6D and SF-36 are other instruments with similar purpose. Although there are doubts about the interchangeability of the two instruments, they are often used either together or separately [15].

### **2.2.2 Costs**

Costs in health economic analyses are commonly divided into two or three categories.

First, direct costs are costs of hospital visits, outpatient care, procedures, diagnostics, devices and other services. Non-medical related costs are also often included, such as transportation costs and social assistance.

Indirect costs are costs that usually are not paid directly but arise nonetheless. These are chiefly productivity loss due to the illness, such as the foregone production because of absence from work or early retirement.

The third category sometimes included, is the valuation of non-monetary effects of illness or its treatment. Mainly, this refers to calculations where QALYs are assigned monetary value.

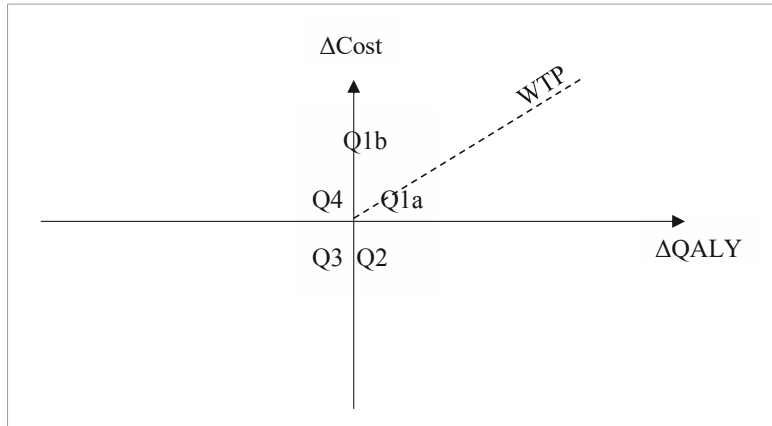
The perspective of the study is an important factor in the design and interpretation. Some have a societal perspective, where all costs are counted regardless of where they accrue, while other have a health care perspective, where only costs related to the health care system are measured. The latter would exclude indirect and intangible costs [16].

### **2.2.3 Cost-effectiveness**

Cost-effectiveness refers to the relationship between costs and effectiveness. In health economic analyses, effectiveness is measured with QALYs. When two mutually exclusive treatments are compared, the difference in costs is divided by the difference in QALYs. The result is called the incremental cost-effectiveness ratio (ICER). An ICER can be interpreted as being the price at which QALYs can be created. Whether an ICER is high or low depends on the decision-

maker's willingness to pay (WTP) for a QALY. The ICER from such calculations can be plotted on a cost-effectiveness plane.

Figure 1: Cost-effectiveness plane. The plane shows the difference between two treatments being compared, where



one of the treatments—the control—is at the intersection between the two lines with coordinates  $[0,0]$ . If the other treatment is cheaper and creates more QALYs, it falls into quadrant 2. Such treatments are said to be dominating as they should be adopted immediately. Treatments that are more expensive and create net loss of QALYs fall into quadrant 3. These are said to be dominated and should be avoided. A line in Q1 shows the trajectory of the willingness to pay (WTP). Treatments that fall into Q1a are below the line and thus provide adequate value for money, while treatments above the line are too expensive to be adopted at the given WTP. Treatments falling into quadrant 3 are difficult to interpret, as it involves decreasing the service provided to save money.

Cost-effectiveness studies of treatment of LBP are presented in chapter 2.4.

#### 2.2.4 Burden and cost of illness

Cost of illness (COI) is a type of study intended to measure the economic burden of disease on the whole population. Usually, COI include direct costs and indirect costs as measured in loss in productivity related to the illness in question. Also, COI can comprise non-economic factors such as loss in QALYs, where the loss in QALYs are translated into monetary values.

Studies of this kind are both conducted on specific diseases and on whole disease burden on societies. This can be exemplified in the Global Burden of Disease project which both includes holistic view on disease burden [17] and dives into specifics of for example LBP[4].

COI studies can be used to draw attention to particular health problems and encourage policy debate, and also to inform planning of healthcare services, the prioritization of prevention research and the evaluation of policy options [18]. Such studies give no direct guidance of how resources should be allocated to improve efficiency. However, they can give information about the total societal burden which can be important when determining what attention and awareness the disease should be given in, for example, public health interventions.

Also, COI studies can map who and to what extent different stakeholders bear the burden of disease—be it the healthcare sector, the patients or the employers. As such, COI studies can be the building block on which both academia and the health care sector can build to improve decision making.

For details on the burden of LBP in particular, see chapter 2.5, *Economic burden*.

### **2.2.5 Modelling in health economics**

Health economic models are mathematical frameworks that relate the course of the illness to the use of the alternative interventions and other factors. By using such a model, the often-limited clinical trial data can be extrapolated to longer periods of time, other populations and different practices than those studied in the trial. Also, expected costs and impact on QoL can be added. The models also allow for the quantification of uncertainty around estimates [19].

The simplest form of models are decision trees, where two or more possible outcomes or choices are compared. These can be made more elaborate by adding branches to the tree, adding probabilities and thus make possible the calculation of expected values. However, this framework quickly becomes too simplistic, especially when looking at long time horizons and many different outcomes.

The usual answer to the shortcomings of decision trees is to construct Markov cohort models. These take a time horizon, from a few months up to years or decades, and divide these into discrete cycles. Possible outcomes are grouped into states, each assigned an outcome of QoL and cost. Transition probabilities are used to transfer the starting cohort between states at the end of each cycle. By summing up QALYs and costs over all states and cycles, different treatments can be assessed.

Markov cohort models have long since become a standard in the health economist's toolbox, in part due to their versatility and ease of extensions. However, depending on the treatment and disease progression, even these can become too simplistic. Particularly, if the number of states becomes too high or if states, cycles and transition probabilities need to be dynamic. In particular, when patient history needs to be taken into account, individual-level microsimulation methods are often required [19, 20].

Patient-level simulations come in many forms, some adapting methods from engineering and production optimisation. These can either be in continuous time or discrete time, the former usually take the form of discrete event simulations. The latter can in some ways be similar to Markov cohort models, except integrating patient history and only following one patient through the model each time, and then repeating the exercise thousands of times. An individual state model was used in paper II.

## **2.3 RANDOMISATION AND REAL-WORLD DATA**

As this thesis consists both of results from randomised studies and real-world data, their relative strengths and weaknesses should be discussed.

Randomised controlled trials (RCTs) are regarded as the gold standard in medical research. The randomisation—in conjunction with blinding and other methods—is intended to ensure that no confounders or bias are present and that effects can be assigned to their respective treatment rather than circumstances or chance.

However, RCTs, particularly for surgical interventions, have their drawbacks. First, they derive data from often tightly controlled environments, where stringent inclusion and exclusion criteria are used to select a patient population that may be a biased sample of the whole population. Second, they create an artificial environment that does not always represent real-world practices. Third, contrary to placebos in pharmacological studies, it is problematic to conduct placebo-surgeries (often referred to as sham procedures), both for ethical reasons, but also because of the difficulty of designing a procedure that masks for the patient which group he/she was randomized into, but at the same time does not constitute a treatment.

RCTs are in general—and quite importantly for health-economic evaluations—often limited in time and of a limited scope. This is a problem as all relevant costs and effects should be captured by such an evaluation, wherever and whenever they incur, as long as they are relevant to the treatment under consideration. Survival benefits in the future or long-lasting effects of a particular treatment regimen are thus not captured in for example a 2-year long study, skewing cost-effectiveness from expensive and long-lasting treatments to cheap ones with short-term effects.

These reasons, along with high costs of conducting RCTs, have contributed to a rise in interest in real-world data (RWD). By combining registers, both medical registers and various government data, real-world data can answer questions where RCTs are not feasible. Also, such studies can be used to validate results from RCTs. Studies that have compared RCT-derived data to RWD have shown that the two approaches can give comparable results if data is used in a scientifically sound manner [21].

### **2.3.1 Analysing crossover and drop-outs**

When analysing results from RCTs, specific statistical problems arise when the study protocol is not followed. Of these, two problems and their solution will be mentioned here.

First there is the crossover. In the context of RCTs with treatments A and B, crossover is when patient assigned to treatment A does not receive the treatment, either receiving treatment B, a different treatment or none at all. This can have profound effect on the results, the most famous example within LBP probably being the SPORT trial where 50% of patients assigned to surgery received surgery within 3 months of enrolment, while 30% of those assigned to nonoperative treatment received surgery in the same period [22].

The way to analyse such cases is to use *intention to treat* analysis (ITT). This dictates that patients should be analysed using their assigned group. The other approach, *per protocol* (PP), is to analyse according to treatment received.

Arguably, patients who do not follow their randomized treatment are in one way or another different from the rest of their treatment group. Some of these differences can be observed. However, unobserved differences cannot be ruled out; indeed, it is quite likely that patient characteristics dictate whether they follow protocol or not. For this reason, ITT analysis is considered the gold standard in health economic evaluations [23].



Additionally, questions in health economics often are about what policy health authorities should adopt and which should be rejected. In this sense, the question is not whether a surgery works, but whether *the decision to operate surgically* is a good policy or not, regardless of whether the patients receive the operation or not. This view has parallels in studies of self-administered drugs. There, the interesting question from a health economic perspective is whether *prescription* of drug is cost-effective rather than the narrower *use* of drugs.

## 2.4 COST EFFECTIVENESS

In a literature review, detailed in chapter 4.2, 57 articles were identified. Of these, 11 considered cognitive behavioural therapy or other psychological treatments, four pharmacological treatments, 14 surgical treatments, 14 physiotherapeutic treatments, 23 other non-surgical interventions and six alternative medicine. The vast majority described treatments to non-specific LBP or 52, while three mentioned stenosis, two disc herniation, four degenerative disc disease and seven other specific conditions (some looked at more than one diagnoses, hence the sum higher than 57). Papers commonly looked at more than one form of treatment and/or more than one form of conditions, so the sum is higher than the number of papers.

The results of Andronis et al. [24], who also systematically reviewed evidence on cost-effectiveness of non-surgical treatments were that “combined physical and psychological treatments, medical yoga, information and education programmes, spinal manipulation and acupuncture are likely to be cost-effective options for LBP.” The cost-effectiveness of physical exercise programs are less certain.

No simple messages can be extracted from the review. This stems from the difficulty of diagnostics, the complex nature of the underlying ailments and methodological hurdles among other things. The relative lack of literature in the field, given the immense burden, is however a matter of concern.

## 2.5 ECONOMIC BURDEN

Pain in back and neck is the fourth most burdensome disease category, as measured with disability-adjusted life years (DALYs). In the developed world, where communicable diseases have largely been eliminated, spinal ailments top the lists in most countries [17]. Indeed, out of all 291 conditions studied in the global burden of disease study, LBP was the most burdensome in terms of disability and sixth in terms of overall burden [4]. The difference between the two measures was that the former measured disability in living people, while the latter the burden both in disability and lost life years. LBP is not in itself a cause of premature mortality, thus the resulting difference. In Sweden, the number of disability adjusted life years lost per capita increased by 0.065% annually over the last 25 years, according to the same study [17].

Importantly, however, these numbers do not consider costs, neither direct nor indirect.

LBP was the largest diagnosis group in all paid short term sick leave benefits in Sweden in 2001 [25]. LBP is very common, and at any given point in time, 15–30% of the population suffers

from the disorder while 60–80% of the population has at some point in life suffered from the condition [26–28] Despite its considerable contribution to disability worldwide, the attention LBP has received has delivered less than optimal improvement for those affected on a group level.

In addition to direct treatment costs, indirect costs, such as productivity loss and costs associated with care provided by relatives stack up to a high aggregated cost. Using a top-down approach the burden of LBP in Sweden has been estimated at €1,860 million in 2001 prices, where indirect costs accounted for 84% of total cost [8]. As a comparison, in 2014 prices, burden per capita per year has been estimated to approximately €410 in Europe [29] and €317 in Australia [30].

## **3 AIMS OF THE THESIS**

### **3.1 GENERAL AIMS**

The objective of this thesis is to enhance the understanding of the economic aspects of low back pain (LBP), including lumbar disc herniation (LDH) and lumbar spinal stenosis (LSS).

The overarching research themes are two:

- What is the burden of LBP in Sweden?
- Are surgical interventions for LBP cost-effective?

### **3.2 SPECIFIC AIMS**

However, these questions are very broad and cannot be fully answered in a single thesis, in particular the second one. Thus, these two questions are answered with two papers each with narrower scope and aims.

#### **3.2.1 Cost of low back pain (paper I)**

To estimate the societal costs of low back pain with or without radiating leg pain.

#### **3.2.2 Treatment pathway model (paper II)**

To develop a health economic model to evaluate the long-term costs and outcomes over the healthcare treatment pathway for patients with LBP.

#### **3.2.3 Cost-effectiveness of total disc replacement in patients with chronic low back pain (paper III)**

To evaluate the cost-effectiveness of total disc replacement (TDR) versus multidisciplinary rehabilitation (MDR) in patients with chronic LBP.

#### **3.2.4 Cost-effectiveness of fusion in decompression surgery for lumbar spinal stenosis (paper IV)**

Determine whether decompression plus fusion (DF) is cost effective compared with decompression alone (D) in lumbar spinal stenosis, with or without degenerative spondylolisthesis.

## 4 REVIEW OF LITERATURE

The thesis is comprised of four sub-studies, all tied together with the common thread of the title, health economic aspects of low back pain and lumbar spinal stenosis.

Each study, however, covers a specific aspect of this broad theme and contributes in different ways to the research frontier. The literature review is thus structured in two parts; recent research in assessment of the burden of LBP and LSS and the cost-effectiveness of interventions.

### 4.1 BURDEN OF LOW BACK PAIN

A systematic literature search was made to identify literature studying burden of low back pain. The search was confined to research published in the last 15 years in English, and as MeSH terms were used, was confined to Medline/Pubmed. The search identified articles about the economic aspects of low back pain, adding the constraint of including the word *burden*<sup>1</sup>. Studies that focused on a single or a subset of treatments or diagnoses were excluded in title and full text review. Only papers in English were included.

A PRISMA flowchart is presented below with an overview of the identified literature.

The identified literature was divided into three categories; global assessments of burden, systematic reviews, and regional and local assessments, as detailed in Table 1.

---

<sup>1</sup> "Low back pain/economics"[mesh] "last 15 years"[dp] burden eng[la]

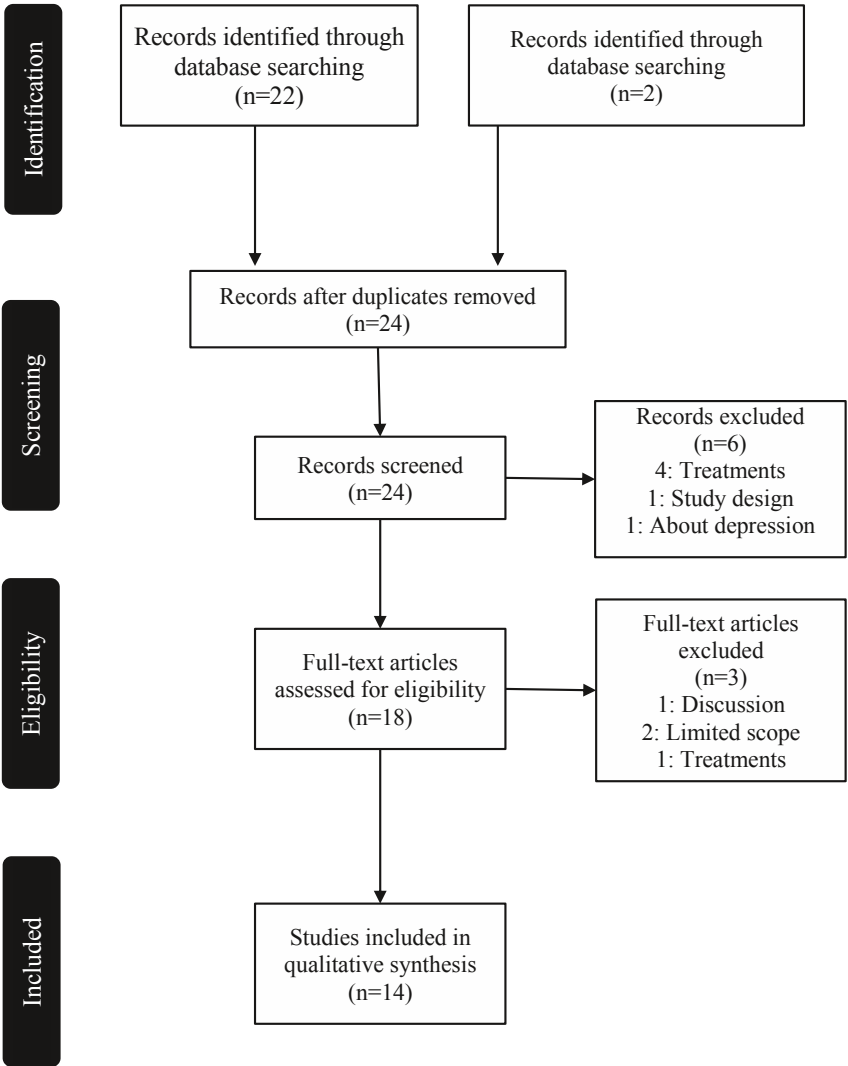


Figure 2: PRISMA flow chart of literature review of burden

Table 1: Results of review of literature about burden in order of publication

First author	Year	Shortened title	Global	Regional	Review
Walker	2003	Low back pain in Australian adults: the economic burden		✓	
Ekman	2005	The economic cost of low back pain in Sweden in 2001		✓	
Ekman	2005	Burden of illness of chronic low back pain in Sweden		✓	
Wasiak	2006	Work disability and costs caused by recurrence of low back pain		✓	
Dagenais	2007	A systematic review of low back pain cost of illness studies			✓
Juniper	2009	Epidemiology, economic burden and pharmacological treatment			✓
Depont	2010	Medical and non-medical direct costs of chronic low back pain in France		✓	
Hoy	2010	The Epidemiology of low back pain.	✓		
Wieser	2011	Cost of low back pain in Switzerland in 2005		✓	
Gore	2012	The burden of chronic low back pain in usual care settings			
Hoy	2012	Review of the Global Prevalence of Low Back Pain			✓
Mehra	2012	Burden of chronic low back pain with and without a neuropathic component			
Hong	2013	Costs of treatment of chronic low back pain: an analysis of the GPRD		✓	
Itoh	2013	Annual medical costs of work-related low back pain in Japan.		✓	
Hoy	2014	The global burden of low back pain	✓		
Murray	2015	Global, regional, and national DALYs for 306 diseases and injuries	✓		

#### 4.1.1 Global assessments of low back pain

According to the global burden of disease-project, pain in back and neck is the fourth most burdensome disease category, as measured with disability-adjusted life years (DALYs). In the industrialised world, where big strides forward have been made in treating communicable diseases and heart diseases, spinal ailments top the lists in most countries [17].

Indeed, out of all 291 conditions studied in the global burden of disease study, LBP was the most burdensome in terms of disability and sixth in terms of overall burden [4]. The difference between the two measures was that the former measured disability in living people, while the latter the burden both in disability and lost life years. LBP is not in itself a cause of premature mortality, thus the resulting difference.

For number of years lived with disability, LBP ranked first place in almost all regions, going lowest to fourth place in the Caribbean and Southern sub-Saharan Africa. In lost disability-adjusted life-years, it ranked lowest 23<sup>rd</sup> in Central sub-Saharan Africa, but up to first place in both Western Europe and Australasia [4]. The global point prevalence of LBP was estimated to be 9,4%, effectively meaning that in any given year, 9,4% of the world population has LBP. The definition specifies that the pain must be “activity-limiting LBP (with or without pain in lower limbs) that lasts for at least one day”.

Although thorough, the global burden of disease studies involved a range of guesswork, both generally and for LBP specifically. Its main conclusion, however, is that by using standardised measures and by looking globally, the real burden can be assessed. Subsequently, research and clinical priorities can be adjusted, and although no formal assessment has been found, there does seem to be a lack of research on LBP seen in relation to its burden. Subsequently, Hoy et al.[4]—repeating a pattern common in other literature on the subject—claim that there is an “urgent need for further research to better understand LBP across different settings.”

This lack of research can be seen in the epidemiological literature, where estimates of one-year incidence range from 1.5–36% and recurrence at 1 year range from 24–80%. These wide ranges can in big part be attributed to differences in definitions [26].

#### 4.1.2 Reviews

Dagenais et al. [31] published in 2008 another systematic review of cost of illness studies from 1997 to 2007. Stating wide differences in methodology, it showed that by any measure, the burden was considerable. The study found total 27 relevant studies with cost per capita ranging from less than a dollar (48 JPY in 1994) to 500 today’s dollars (474 AUD in 2001). The authors found the lack of a study of LBP’s total societal burden in the USA to be especially glaring, potentially yielding a sub-optimal devotion of resources aimed at the field. Among the conclusions was that lowering indirect costs may be the best opportunity to lower the costs of LBP.

Disparaging methodologies between studies was one of the main conclusions of a paper by Hoy et al. [32]. However, at this point, a set of recommendations put forth in a Delphi study from 2008 [33], in particular how prevalence studies should define LBP. This paper focused on the only on the prevalence of LBP would later become a part of the global burden of disease mentioned above. It included both a more global search for publication, an attempt to assess risk of bias and more specific definitions than previous reviews. A multivariate analysis showed that prevalence was higher among females than males, similar between urban and rural populations, and almost two times higher in high income countries as compared to low income countries.

Juniper et al. [34] studied the epidemiology, economic burden and pharmacological treatment of chronic LBP in France, Germany, Italy, Spain. In assessing the economic burden, they also conducted a literature review. For resource utilization, the study found four studies and for indirect cost estimates three studies, one for Germany, Spain and the UK each. All studies were small, methodologically limited and by now outdated.

### **4.1.3 Regional and local assessments**

#### *4.1.3.1 Sweden*

Two studies from the same research group were identified that present burden estimates for Sweden. One focused solely on costs and used a top-down approach [8], while the other used survey data and bottom-up approach [9], with the latter including also a measure of quality of life. The bottom-up approach suffers from low response frequency (9%) of patients recruited at outpatient care facilities in Sweden. The average annual cost of chronic LBP per patient was estimated at €20,700, of which 85% were indirect costs. Based on this, the authors found it particularly important to find treatments that reduce the high costs of sick leave and early retirements because of chronic LBP.

The top-down approach included inpatient and outpatient care, prescriptions and indirect costs, both short-term and long-term. Again, indirect costs accounted for 84% of the total burden. Intangible costs (cost of lost quality-adjusted life-years) were also calculated, with the authors finding the total cost to be five times higher. Intangible costs are usually not included in base case analyses of such research but can be instructive in assessing the value of eradicating a disease.

#### *4.1.3.2 Other European countries*

Using data from the United Kingdom General Practice Research Database, Hong et al. [35] calculated costs associated with the treatment of chronic LBP. Given the available data, the study only looked at direct costs, comparing chronic LBP patients with a matched control group. Of the cost difference amounting to £500, 60% was for consultation by general practitioners, 22% by secondary care and the rest due to pharmaceuticals.



Depont et al.[36] published in 2009 a retrospective, observational, cohort study in primary care in France. The study included around 800 adult patients with chronic LBP between October 2001 and December 2002. The total mean cost per patient over six months was slightly more than €700. Of these, 23% were by physiotherapists and similar specialists, 20% to medications, 17% to hospitalizations, 10% to diagnostics and 13% to physician fees. No attempt was made to collect indirect costs.

Wieser et al. [37] studied LBP in Switzerland in 2005. It was a bottom-up prevalence-based cost-of-illness study with a societal perspective. The data used was a questionnaire completed by a sample of 2,500 around half suffered from LBP in the last 4 weeks and 350 of them were receiving medical treatment for their LBP. Direct costs of LBP were estimated at €2.6 billion and direct medical costs at 6.1% of the total healthcare expenditure in Switzerland. Productivity losses were estimated at €4.1 billion with the human capital approach and €2.2 billion with the friction cost approach. The total economic burden of LBP to Swiss society was between 1.6 and 2.3% of GDP.

The study's main addition to the literature is however its estimates of presenteeism (loss of productivity while at work), as being the single most prominent cost category. As for other data, this was collected using questionnaires, which are said to be reliable when recall periods are short (1 or 2 weeks), and that the link between claimed presenteeism and actual productivity is quite strong.

#### *4.1.3.3 Other*

Mehra [38] looked at US claims database for the years 2006–8, having records for 40 thousand patients, comparing patients with and without neuropathic pain. Of the sample, 90% had neuropathic pain. Mean annual cost of care per patient was 160% higher for patients with neuropathic pain than without (US\$ 2577 and US\$1007 respectively).

This difference between the two groups lead the authors to claim a “greater need for new treatment options that more comprehensively manage the range of pain symptoms and signalling mechanisms involved”.

Wasiak et al. [39] studied workers' compensation claims data for low back injuries in a New Hampshire, USA. The results, based on claims on 1900 workers, indicated that 17% had recurrent work disability and 34% received recurrent care. Recurrences contributed disproportionately to the total burden of work-related nonspecific injuries.

Lastly, Walker et al. [30] estimated the cost of illness in Australia. The total cost was calculated at \$9.2 billion AUD, whereof 89% were indirect costs. The authors say the burden is so great “that it has compelling and urgent ramifications for health policy, planning and research”, where particular focus should be on indirect costs and cost-effective management regimes that encourage an early return to duties.

## 4.2 COST-EFFECTIVENESS OF TREATMENT

Given the high burden of LBP, it is essential to find treatments that are effective, and more to the point here, cost-effective.

The literature search involved searching for evidence of cost-effectiveness of interventions for low back pain. The MeSH-term for cost-effectiveness was deliberately used so as to also include other similar analyses such as cost-benefit and cost-utility analyses. No specific diagnosis was excluded or explicitly included. To limit the size of the literature search, only papers from the last 15 years were included and protocols were excluded. Some measure of quality of life or utility was required to be included, in line with Indrakanti et al. [40]. Only papers in English were included. The search was limited to PubMed. Reviews were included, and ad-hoc inclusion of papers allowed<sup>2</sup>.

Figure 3 shows a PRISMA-inspired flow-chart. Gross number of papers included was 94, with 57 included in the final qualitative review.

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<sup>2</sup> Search string: "Cost-Benefit Analysis"[Mesh] AND "Low back pain"[mesh] "last 10 years"[dp] english[la] NOT protocol[ti] AND ("quality-adjusted" OR "quality of life" OR QALY OR "life years" OR "EQ-5D" OR "SF-6D" OR "SF-36")

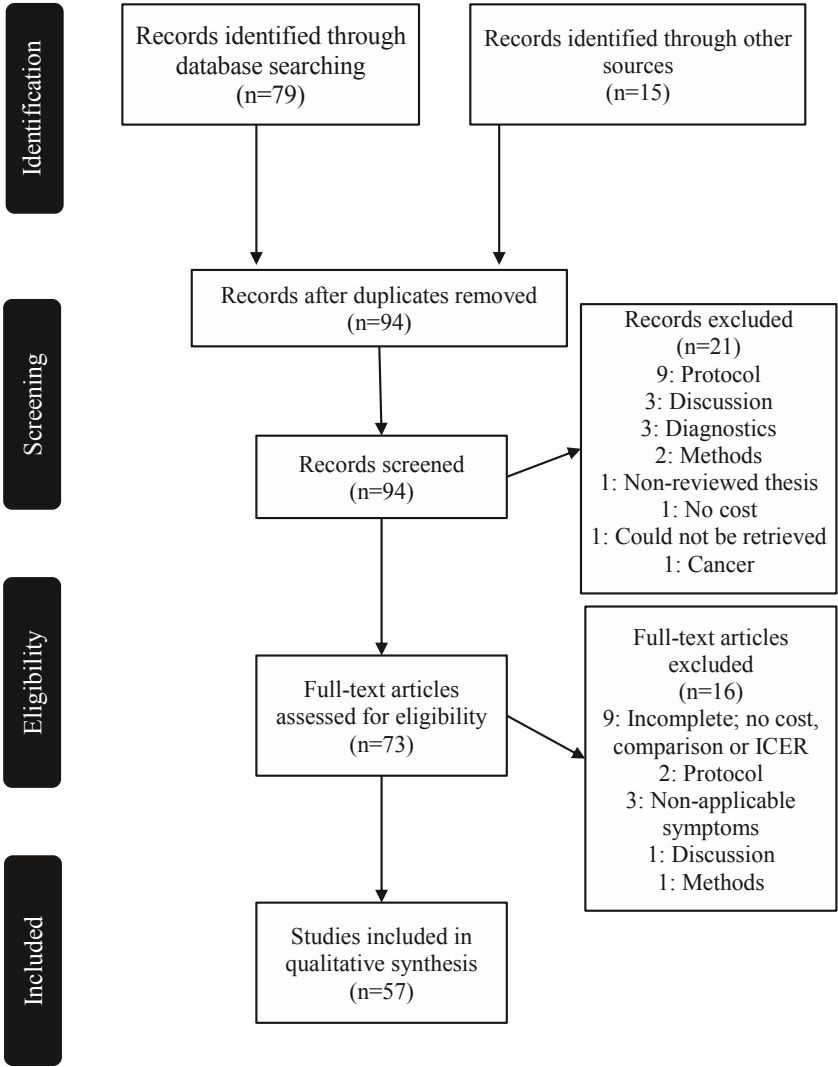


Figure 3: PRISMA flow chart of literature search for cost-effectiveness

Table 2. Results of review of literature about cost-effectiveness ordered chronologically within each treatment category

First author	Short title	Year	Treatment	Type	Diagnosis
<b>Hoijenbos</b>	CE of active implementation strategy	2005	Physiotherapy	Original	Non-specific
<b>Critchley</b>	Effectiveness and CE of three types of physiotherapy	2007	Physiotherapy	Original	Non-specific
<b>van der Roer</b>	CE of intensive group training protocol	2008	Physiotherapy	Original	Non-specific
<b>Smeets</b>	CEA of combined, single behavioral and single physical rehabilitation	2009	Physiotherapy	Original	Non-specific
<b>Fritz</b>	CE of primary care management with or without physical therapy	2017	Physiotherapy	Original	Non-specific
<b>Hahne</b>	Individualized physical therapy is CE	2017	Physiotherapy	Original	Non-specific
<b>Steenstra</b>	Economic evaluation of multi-stage return to work program	2006	Physioth., other non-surg.	Original	Non-specific
<b>Tsertsvadze</b>	CE of manual therapy: systematic review	2014	Physioth., other non-surg.	Review/ MA	Non-specific
<b>Freeman</b>	CE of circumferencial lumbar fusion	2007	Surgical	Original	Non-spec., other spec.
<b>Hansson</b>	CUA of lumbar disc herniation surgery	2007	Surgical	Original	DH
<b>Soegaard</b>	Circumferential fusion is dominant over posterolateral fusion	2007	Surgical	Original	Non-specific
<b>Tosteson</b>	Surgical treatment of spinal stenosis	2008	Surgical	Original	Stenosis
<b>Fritzell</b>	CE of disc prosthesis vs lumbar fusion	2011	Surgical	Original	Non-specific
<b>Parker</b>	CE of minimally invasive vs open transforaminal lumbar fusion	2012	Surgical	Original	DDD, other spec.
<b>Parkinson</b>	CE of lumbar artificial intervertebral disc replacement	2013	Surgical	Original	
<b>Christensen</b>	Transforaminal lumbar interbody fusion vs posterolateral	2014	Surgical	Original	Non-specific
<b>Johnsen</b>	CE of total disc replacement versus multidisciplinary rehabilitation	2014	Surgical	Original	Non-spec., DDD
<b>Weinstein</b>	SPORT value compass	2014	Surgical	Review/ MA	Non-specific

<b>First author</b>	<b>Short title</b>	<b>Year</b>	<b>Treatment</b>	<b>Type</b>	<b>Diagnosis</b>
<b>van den Hout</b>	Prolonged conservative care vs early surgery	2008	Surgical, other non-surg.	Original	Non-specific
<b>Rivero-Arias</b>	Surgical stabilisation compared with intensive rehabilitation	2005	Surgical, physioth.	Original	Non-specific
<b>Jellema</b>	LBP in general practice: CEA of psychosocial intervention	2007	CBT/psych.	Original	Non-specific
<b>Johnson</b>	Active exercise, education and CBT for LBP	2007	CBT/psych.	Original	Non-specific
<b>Lamb</b>	Group CBT for LBP in primary care	2010	CBT/psych.	Original	Non-specific
<b>Lamb</b>	RCT of primary care-based CBT	2010	CBT/psych.	Original	Non-specific
<b>Norton</b>	CU of CBT from the commercial payer perspective	2015	CBT/psych.	Model	Non-specific
<b>Goossens</b>	Is exposure in vivo cost-effective?	2015	CBT/psych.	Original	
<b>Schweikert</b>	Effectiveness and CE of adding CBT	2006	CBT/psych., other non-surg.	Original	Non-specific
<b>Rivero-Arias</b>	CUA of physiotherapy compared to advice	2006	CBT/psych., physioth.	Original	Non-specific
<b>Whitehurst</b>	A brief pain management program compared with physical therapy	2007	CBT/psych., physioth.	Original	Non-specific
<b>Andronis</b>	CE of non-invasive and non-pharmacological interventions	2017	CBT/psych., physioth., other non-surg.	Review/MA	Non-specific
<b>Wielage</b>	CE of duloxetine in CLBP: Quebec perspective	2013	Pharmac.	Original	Non-specific
<b>Wielage</b>	CE of duloxetine in CLBP: US private perspective	2013	Pharmac.	Original	Non-specific
<b>Haas</b>	Pharmacological management of CLBP: review of CE	2015	Pharmac.	Review/MA	Non-specific
<b>Thomas</b>	Longer term benefits of acupuncture	2005	Alt. med.	Original	Non-specific
<b>Ratcliffe</b>	RCT of acupuncture	2006	Alt. med.	Original	Non-specific
<b>Witt</b>	Pragmatic RCT of acupuncture for LBP	2006	Alt. med.	Original	Non-specific
<b>Herman</b>	CE of naturopathic care	2008	Alt. med.	Original	Non-specific
<b>Kim</b>	Economic analysis of usual care and acupuncture	2010	Alt. med.	Model	Non-specific
<b>Herman</b>	Are complementary therapies and integrative care cost-effective?	2012	Alt. med.	Review/MA	Non-specific

First author	Short title	Year	Treatment	Type	Diagnosis
<b>Ijzelenberg</b>	Effectiveness of back pain prevention program	2007	Other non-surg.	Original	Non-specific
<b>Bastiaenen</b>	Brief self-management intervention for pregnancy-related LBP	2008	Other non-surg.	Original	Other spec.
<b>Henchoz</b>	CUA of three-month exercise programme	2010	Other non-surg.	Original	Non-specific
<b>Lambeek</b>	Effect of integrated care for sick listed patients	2010	Other non-surg.	Original	Non-specific
<b>Roelefs</b>	CE of lumbar supports for home care workers	2010	Other non-surg.	Original	Non-specific
<b>Rogerson</b>	CUA of interdisciplinary early intervention vs lumbar fusion	2010	Other non-surg.	Original	Non-specific
<b>Hill</b>	Stratified primary care management vs current best practice	2011	Other non-surg.	Original	Non-specific
<b>Apeldoorn</b>	CE of classification-based system	2012	Other non-surg.	Original	Non-specific
<b>Chuang</b>	Multicenter RCT of yoga for chronic LBP	2012	Other non-surg.	Original	Non-specific
<b>Whitehurst</b>	Exploring the CU of stratified primary care management	2012	Other non-surg.	Original	Non-specific
<b>Whynes</b>	CE of epidural steroid injections	2012	Other non-surg.	Original	Non-specific
<b>Aboagye</b>	CE of early interventions for non-specific LBP	2015	Other non-surg.	Original	Non-specific
<b>Whitehurst</b>	Implementing stratified primary care management	2015	Other non-surg.	Original	Non-specific
<b>Wilson</b>	Analysis of provider specialties	2015	Other non-surg.	Original	Non-specific
<b>Jensen</b>	Economic evaluation of an implementation strategy	2017	Other non-surg.	Original	Non-specific
<b>Manchikanti</b>	CUA of lumbar interlaminar epidural injections	2017	Other non-surg.	Original	Sten., DH, DDD
<b>Indrakanti</b>	Value-based care in the management of spine disorders	2012	All	Review/ MA	Non-specific

#### 4.2.1 Physiotherapy

Tsertsvadze [41] conducted a systematic review of trial-based economic evaluations of manual therapy relative to other alternative interventions used for the management of musculoskeletal conditions. Six trials were identified for LBP. Manual therapy techniques (e.g., osteopathic spinal manipulation, physiotherapy manipulation and mobilization techniques, and chiropractic manipulation with or without other treatments) were more cost-effective than usual general practitioner care alone or with exercise, spinal stabilization, GP advice, advice to remain active, or brief pain management for improving low back pain/disability. The authors caution however that at present there is a paucity of evidence on the cost-effectiveness evaluations for manual therapy interventions. Further improvements in the methodological conduct and reporting quality of economic evaluations of manual therapy are warranted in order to facilitate adequate evidence-based decisions among policy makers, health care practitioners, and patients.

Hoeijenbos et al. [42] compared whether actively implementing an evidence-based physiotherapy guideline for non-specific low back pain to the standard method of dissemination. Measuring both quality of life and costs, no discernible effect was seen on neither costs, productivity nor utility, rendering the active implementation not cost-effective.

Critchley et al. [43] used a pragmatic, randomized, assessor-blinded, clinical trial to compare the effectiveness and cost-effectiveness of three kinds of physiotherapy common in treatment of LBP. More than 200 patients were randomized to spinal stabilisation classes, physiotherapist-led pain management or usual outpatient physiotherapy.

Although all regimens improved outcomes, the cost-effectiveness was best for the physiotherapist-led pain management, giving a chance for cost-reduction without threatening patient outcomes.

Rivero-Arias et al. [44] report from an economic evaluation alongside a pragmatic randomized controlled trial, conducted to compare routine physiotherapy with an assessment session and advice from a physiotherapist for patients with LBP. Almost 300 patients were enrolled. Although health care system costs were not significantly different, out-of-pocket expenses were, favouring the advice group. Utility levels improved similarly in both groups, suggesting that advice given by a physiotherapist should be considered as the first-line treatment for patients with LBP.

Smeets et al. [45] examined whether a combination of a physical training and operant-behavioural graded activity with problem solving training is cost-effective compared to either alone at one year after treatment. 172 patients with chronic disabling non-specific LBP, were randomized to a course of active physical treatment, psychological treatment or a combination of both. The psychological treatment turned out to be cost-effective, the physical therapy less so, while the combined therapy was not cost-effective.

Steenstra [46] evaluate the cost-effectiveness of a return-to-work program for workers on LBP-induced sick-leave. The trial randomized patients to either a workplace intervention implemented between 2 to 8 weeks of sick-leave with usual care, and a clinical intervention after 8 weeks of sick-leave with usual care. The authors summarise the findings as follows “the workplace intervention results in a safe and faster RTW than usual care at reasonable costs for workers on sick-leave for two to six weeks due to LBP.”

Van der Roer and colleagues [47] evaluated the cost effectiveness of an intensive group training protocol compared with usual care physiotherapy in patients with nonspecific chronic LBP. The intensive group training protocol combines exercise therapy, back school, and behavioural principles. After 1 year, the group that received the intensive treatment had accrued higher direct costs the direct health care costs were similar, as were outcomes, yielding rather inconclusive cost-effectiveness estimates. The authors recommended however that the intensive group training protocol not be implemented at a national level, opting rather for the less-intensive version in the absence of better evidence.

Whitehurst [48] calculated the cost effectiveness of a brief pain management program targeting psychosocial factors compared with physical therapy for primary care patients with early LBP, with 200 patients in each group. There were no statistically significant differences in mean health care costs or outcomes between treatments. Statistically insignificant differences were in favour of physical therapy on the utility side, but on the pain management on the cost side. The calculated incremental cost-per-QALY ratio indicated that there is only a 17% chance that brief pain management provides the best value for money. Physical therapy is a cost-effective primary care management strategy for low back pain. However, the absence of a clinically superior treatment program raises the possibility that a combined therapy could be considered.

Fritz et al. [49] conducted a study comparing whether early physical therapy was cost-effectiveness or not. The addition of physical therapy increased both costs and quality of life, with an acceptable ICER, leading the authors to claim the addition to be cost-effective for patients with acute, nonspecific LBP.

Hahne et al.[50] studied whether individualized physical therapy is a better use of money than the traditional guideline-based advice. The study included 300 people randomly assigned to either two guidelines-based sessions or ten individualized. Interestingly, total costs were similar, but the individualized regime created significantly better results.

Given these conclusions, the study mentioned above that looked into combined psychological and physical therapy did not indicate that the combination is cost-effective [45]. Likely, the results of such programs vary on the patient population and details of the interventions.

Andronis et al. [24] systematically reviewed evidence on cost-effectiveness of non-surgical treatments and found that “combined physical and psychological treatments, medical yoga, information and education programmes, spinal manipulation and acupuncture are likely to be



cost-effective options for LBP.“ The cost-effectiveness of physical exercise programs are less certain.

## **4.2.2 Surgical procedures**

Evaluations of surgical procedures can be divided into those comparing similar surgical procedures, and those comparing surgery with non-surgical management.

### *4.2.2.1 Lumbar Spinal Stenosis*

Tosteson [51] reported on outcomes of surgery over 2 years among patients with stenosis with and without degenerative spondylolisthesis, with non-operative care as a control. Among 634 patients with stenosis, 62% had surgery, most often decompressive laminectomy. Stenosis surgeries improved health to a greater extent than nonoperative care (0.17 QALYs) at a cost of \$77 600 per QALY gained. Degenerative spondylolisthesis surgeries significantly improved health versus non-operative care (QALY gain, 0.23), at a cost of \$115 600 per QALY gained. The authors concluded that the economic value of spinal stenosis surgery at 2 years compared favourably with many health interventions. Lastly, the authors conclude that surgery for degenerative spondylolisthesis surgery is “not highly cost-effective over 2 years but could show value over a longer time horizon”.

As a part of the same research project, Weinstein et al. [52] reported on the cost-effectiveness calculations based on results from the seminal SPORT-study. At 4 years’ follow-up the ICER for surgery was \$20,000, \$59,000 and \$64,000 per QALY for disc herniation, spinal stenosis and degenerative spondylolisthesis respectively. The first one is usually regarded as cost-effective, while the second two are more doubtful.

### *4.2.2.2 Lumbar Disc herniation*

In Hansson [53], 92 individuals in a cohort of more than a thousand Swedish subjects underwent lumbar disc herniation surgery, where each surgical patient was matched with a patient treated conservatively. Direct costs were much higher for surgical treatment with indirect costs being lower. The median QALYs gained were 0.363 for surgical cohort and 0.036 for those receiving conservative care, and with low difference in total costs, Surgery for lumbar disc herniation was deemed cost-effective.

### *4.2.2.3 Surgery and non-specific conservative treatment*

In patients with chronic LBP Johnsen et al.[54] compared surgical intervention of total disc replacement with multidisciplinary rehabilitation. The surgical intervention yielded higher QALYs (0.34), but although the surgery was more expensive up front, the cost addition was recuperated in lower follow-up costs, particularly indirect costs. As the quality of life was different at the end of the follow-up, longer study period is needed to accurately assess the total cost and outcomes.

Rivero-Arias [55] inspected the cost-effectiveness of surgical stabilisation compared with a programme of intensive rehabilitation for the management of patients with chronic LBP by analysing data from an RCT. In short, the surgery was costlier, and although the outcomes were slightly better, the improvement was not deemed cost-effective. One aspect of the study was considerable crossover between treatment arms. If the proportion of rehabilitation patients requiring subsequent surgery continues to increase, the cost-effectiveness of the surgical intervention could be impacted somewhat.

Van den Hout et al.[56] compared early surgery with prolonged conservative care in terms of cost-effectiveness in patients with sciatica caused by lumbar disc herniation. Surgical treatment was more expensive for the health care system, but savings in indirect costs negated the cost increase almost entirely. Surgery, leading to better clinical outcomes, should thus not be withheld for economic reasons.

#### *4.2.2.4 Surgical techniques*

Parker [57] reported on a study comparing minimally invasive lumbar fusion compared to open surgery for patients with degenerative disc disease. Only 15 patients were in each group and differences between them did not reach statistical significance.

Lumbar artificial intervertebral disc replacement (AIDR) were compared by Parkinson et al. [58] with lumbar fusion for the treatment of patients suffering from LBP and or radicular pain who have failed conservative treatment. Five different fusion approaches were tried in this study, that was based on published effectiveness data synthesized in a Markov model. The artificial discs were found to be cost-saving compared with fusion overall (\$1600/patient); however, anterior lumbar interbody fusion and posterolateral fusion were less costly. As a result, the ICER depends on the outcome considered and the comparator. The artificial discs are thus potentially cost-saving.

In 2-year RCT, Christenen [59] compared the cost and utility of transforaminal lumbar interbody fusion to that of posterolateral instrumented fusion. The former method is a newer one with a prospect of lower complication rate. However, the study did not show any difference, neither in cost or outcomes, between the two methods. Subsequently, the authors conclude that transforaminal lumbar interbody fusion “does not seem to be a relevant alternative to PLF from a socioeconomic point of view.”

Freeman [60] compared two techniques in lumbar fusion, titanium cages and femoral ring allografts. The study showed that titanium cages was not cost-effective. In fact, the allografts were both cheaper, better and patients returned to work quicker.

Soegaard [61] reported on a cost-utility evaluation of an RCT with 4- and 8-year follow-ups of circumferential fusion versus posterolateral fusion for LBP. In short, the former method was shown to be dominant.

Fritzell et al. [62] reported on an assessment of the cost-effectiveness of total disc replacement when compared with instrumented lumbar fusion. Social and healthcare perspectives after 2 years are reported. In all, 152 patients were randomized to each group, and at the 2-year follow-up the result was similar in both groups.

#### **4.2.3 Psychological treatments including cognitive behavioural therapy**

Norton [63] conducted a CUA of CBT for the treatment of persistent non-specific LBP from the perspective of US commercial payers using a Markov model. The analysis revealed an acceptable cost for the treatment, and the results were robust across numerous sensitivity analyses.

Psychosocial factors appear to be of importance in the development and prognosis of LBP. As reported by Jellema [47], more than 300 patients with non-specific subacute LBP were randomized to psychological intervention or usual care. Differences in clinical outcomes between both the groups were small and not statistically significant. Differences in costs were however in favour of the psychological intervention. However, the complete case analysis and the sensitivity analyses with imputed cost data were inconsistent with regard to the statistical significance of this difference in cost data, and as a result, the cost-effectiveness is uncertain. Given the uncertainty, the authors conclude that usual practice should not be changed.

Johnson et al. [64] set up an RCT to study whether a group program of exercise and education using CBT reduces pain and disability over a subsequent 1-year. Also, the study was set up to estimate cost-effectiveness of the intervention. The intervention arm received a program of eight 2-hour group exercise session over 6 weeks comprising active exercise and education delivered by physiotherapists using a CBT approach. Both arms received an educational booklet and audio-cassette. The intervention showed only a small and nonsignificant effect at reducing pain and disability with low additional cost. The estimated ICER was £5000/QALYs. Although being cost-effective, the intervention produces only modest improvements in pain and disability.

Lamb et al. published in 2010 papers [65, 66] an RCT with 700 patients where patients were randomised to receive active management (a non-surgical program intended to keep patients active), and active management plus a version of CBT. A year after randomization, 60% of the combined program reported some or complete recovery, compared to 31% in the control group. The intervention was cheap with an ICER of only £1786.

Schweikert et al. [67] investigated return to work and cost-effectiveness of the addition of cognitive-behavioural treatment to standard therapy compared to standard 3-week inpatient rehabilitation for patients with chronic low back pain. More than 400 patients were randomly assigned to usual care or usual care plus cognitive behavioural treatment.

Between groups, there were no significant differences in quality-adjusted life-years gained or in direct medical or nonmedical costs. The cognitive behavioural treatment showed lower

indirect costs. Adding a cognitive behavioural component to standard therapy may reduce work days lost and thus decrease indirect costs.

Gossens et al. [68] compared exposure in vivo (EXP) to more commonly-used graded activity. EXP is a method in which patients are trained to overcome their fear of pain and thus increase their freedom of movement. This is because patients often overestimate the threat of pain. EXP showed a tendency to reduce disability, increase quality adjusted life years and decrease costs compared to graded activity. Based on these results, the authors suggest implementing EXP for this group of patients seems to be the best decision.

A paper comparing psychological treatments to other treatment alternatives have been mentioned above; Whitehurst [48] discussed above showed physical therapy to be superior to psychological intervention.

Lastly, Andronis [24] systematically reviewed 33 papers on non-surgical treatment alternatives, and found the evidence inconsistent. The paper deemed it likely, however, that combination of physical and psychological treatments, medical yoga, information and education programmes, spinal manipulation and acupuncture cost-effective.

#### **4.2.4 Pharmacological treatments**

Wielage et al. [69, 70] published two studies, both based on Markov models of the use of duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, compared to non-steroidal anti-inflammatory drugs. The models incorporated official guidelines, meta-analyses of treatment effect on LBP and probabilities of adverse events and found that duloxetine was cost-effective.

Haas [71] conducted a systematic review of these and found seven studies eligible. The authors found the literature of low quality, calling for higher-quality studies, more uniform presentation of results, and robust modelling.

#### **4.2.5 Alternative medicine**

Alternative medicine, also called complimentary medicine, is a contested field within medicine and specifically the treatment of low back pain. Whereas medical yoga can be regarded as physical therapy or exercise, the main category of alternative therapy that has been studied in the context of low back pain is acupuncture.

Herman et al. [72] studied naturopathic care (acupuncture, relaxation exercises, dietary advice and a back care booklet) in a small (n=70) study where warehouse workers were randomized to either naturopathic care or standardized physiotherapy education and a back care booklet. Witt et al. [73] randomized patients into big groups of 1500 each where half got acupuncture plus normal treatment while control group did not receive acupuncture. Kim et al. [74] synthesize available evidence and include in a model and find acupuncture in conjunction with other therapy to be cost-effective in Korean setting. Thomas [75] and later Ratcliffe et al. [76] report results from the same randomized controlled trial that show

acupuncture to be tolerable, cheap and effective, together making a short course of the treatment to be cost-effective.

### **4.3 OTHER NON-SURGICAL**

A range of other studies have been published that go beyond specific treatments. These will be described very briefly.

#### **4.3.1 Exercise and self help**

Henchoz [77] assessed a three-month exercise program after multidisciplinary rehabilitation showed little effect compared to control group. Both Aboagye [78] and Chuang [79] found the relatively cheap intervention of yoga to show signs of being cost-effective. Bastiaenen meanwhile [80] looked at such interventions for pregnant women and came to inconclusive results.

#### **4.3.2 Prevention**

Rogerson et al. [81] investigated early interventions for high-risk acute LBP patients and found encouraging results. Meanwhile, Ijzelenberg studied whether back pain prevention was cost-effective over a range of occupations and found no support for that [82].

#### **4.3.3 Other**

Roelofs [83] inspected whether lumbar supports were effective in preventing work loss in patients with history of LBP, and found weak evidence in favour of the supports. Both Whynes et al. [84] and Manchikanti et al. [85] found epidural injections to have acceptable cost-effectiveness.

#### **4.3.4 Health care provision and structure**

Given the multi-faceted nature of LBP and how spread out the treatment is, studies on the structure of health care provision are of potential value. Apeldoorn et al. [86] shows that a classification-based system was not cost-effective. Stratified primary care, however, has repeatedly been found to be cost-effective, such as by Hill et al. [87] and two studies by Whitehurst et al. [88, 89]. Providing integrated care with a clinical occupational physician coordinating the care and communication has also shown promise as compared to care according to the current treatment guidelines [90].

Wilson [91] compared costs and outcomes depending on specialties of the health care professionals, and found costs to vary significantly as well as outcomes. The non-randomized nature of the study makes the results difficult to interpret. Lastly, Jensen and colleagues [92] studied how clinical guidelines are implemented, and found multifaceted approach to be superior to usual implementation strategies.

## 5 MATERIALS AND METHODS

### 5.1 BURDEN OF LOW BACK PAIN IN SWEDEN (COMMON FOR PAPERS I AND II)

Papers I and II were both part of the same project. Shared methods are presented first, and then each paper's specific methods are described in turn.

#### 5.1.1 Ethics approval

The study was approved by the Stockholm Regional Ethics Vetting Board, decision 2013/2225-31/5 from 6<sup>th</sup> February 2014.

#### 5.1.2 Data

A research database was assembled from several different data sources as detailed below. The study population was based on people living in Västra Götaland region (VGR) in Sweden, with a population of 1,6 million or around 15% of Sweden's population. All use of data was in accordance with the Swedish law on personal data, *Personuppgiftslagen*, 1998:204. The data sources are described in turn.

##### 5.1.2.1 County-council database VEGA

All health care production in region VGR is reported by health care providers to an administration database (VEGA). It contains patient-level data in both inpatient and outpatient setting, both to specialist and primary care and both from public and private health care providers.

Administration databases were used to identify patients in the study. Additionally, data was used to analyse patient history, disease progression, resource utilization and health outcomes.

##### 5.1.2.2 Quality-of-care register: Swespine

The Swedish quality-of-care register for spinal surgery is called Swespine and is maintained by the Swedish society of spinal surgeons. Swespine registers patients' health status before operation, details about the operation and collects health status at 1, 2, 5 and 10 years after operation. Health status information includes quality-of-life data measured by various instruments such as EQ-5D.

##### 5.1.2.3 Population and activity register (LISA), Statistics Sweden

Statistics Sweden provided socioeconomic factors variables—such as age, income, level of education, civic status and country of birth—on health outcomes and costs. Also, information about when and where people move was extracted.

##### 5.1.2.4 Social Insurance Agency register

Data was extracted describing use of social insurance on an individual basis, most notably absence from work. The database includes ICD codes with reason of absence from work,

which gives indications of the relative impact of LBP compared to other causes of absence. Only absence from work extending the sick-pay period of 14 days are registered in the register as shorter spells are covered by the employer and employee. No central data exists for work loss in spells shorter than the sick-pay periods.

#### *5.1.2.5 Prescription register*

The prescription register, maintained by the National Board of Health and Welfare, includes data on a variety of properties, such as dosage, anatomic therapeutic classification (ATC) codes and costs. The prescription register started in July 2005 in its current form.

#### *5.1.2.6 National patient register*

The National Board of Health and Welfare keeps the national patient register, a national register with information on all inpatient health care visits as well as all outpatient visits where these are not in the primary care sector. Similar data to that in VEGA, but covers larger geographical area and is less detailed.

#### *5.1.2.7 Patient selection*

Patients were included in the study population if the patient visited any health care facility in VGR during the period 2000-12 with an LBP-related cause. A LBP related cause was defined as all lumbar spinal disorders using the following ICD-10 codes: M40, kyphosis and lordosis; M41, scoliosis; M43, other deforming dorsopathies; M46, other inflammatory spondylopathies; M47, spondylosis; M48, other spondylopathies; M51, other intervertebral disc disorders; M53, other dorsopathies, not elsewhere classified; M54, lumbar pain; M99, biomechanical lesions, not elsewhere classified, and Q763, congenital scoliosis due to congenital bony malformation. LBP due to tumour and trauma were not included.

#### *5.1.2.8 Data quality*

These databases are regularly used for research purposes in a variety of disease areas. As such we expect each of these databases to be of relatively high quality and the data easily identified. For example, on average, 98.6% of all inclusions in National Patient Register are entered correctly and the frequency of missing values is very low. The loss of patient information in the Swedish Prescribed Drug Register is very low, according to the register holder. VEGA is administrative and has high quality. The data in the surgical Swespine register are of high quality and have substantial long-term follow-up. Today over 95% of all spine departments register surgeries in Swespine, the number of patients registered at the time of surgery is about 80%, and 1-year follow-up since 2008 is approximately 75%. All these numbers are on a national level, which is unique in an international perspective.

#### *5.1.2.9 Data linkage*

Linkage between data sources was conducted by Statistics Sweden using social security numbers and delivered de-identified. This is illustrated in Figure 4.

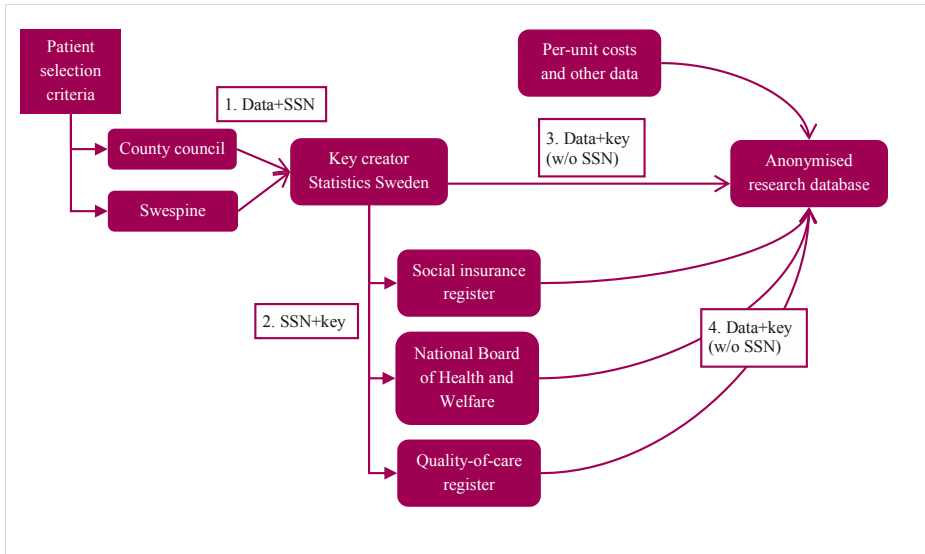


Figure 4: Illustration of the data assembly process. The process starts with sending patient selection criteria to the county council. The county council sends its data with social security numbers to Statistics Sweden. Statistics Sweden does three things; a) it extracts data from its own registers for the given SSNs; b) it creates a key table with all SSNs and keys and sends to other register holders, and c) it sends its data and the data from the county council with SSNs replaced with the key. The other register holders send extract their data based on the SSNs but also replace the SSNs with the key. Upon arriving to the researchers, the data is anonymized but all sharing the same personal key.

#### 5.1.2.10 Technology

Data management Data management was conducted using a MySQL server, statistical analyses using the software package Stata 14, and the model was programmed in Microsoft Excel with Visual Basic for Applications.

#### 5.1.2.11 Unit costs

Unit costs for healthcare resources were collected from Västra Götaland's and other Swedish county councils' regional pricelists where unit cost for a resource item was not available from Västra Götaland [93, 94]. This price list is highly detailed and publicly available, and cost variation across Sweden is deemed small.

### 5.1.3 Prices, currencies and other assumptions

Costs were inflated to the price level of 2016 using consumer price index from Statistics Sweden and presented in Euros (€), converted at the average annual exchange rate for 2016 of 9.47 Swedish Krona per Euro.

Our data included all visits to primary and secondary care in the Västra Götaland county, 1.6 million inhabitants (17% of Sweden's 9.6 million inhabitants). For calculations for the whole Swedish population, the case-mix and demographics were assumed to be the same in Västra Götaland as in the rest of Sweden.



Productivity loss was valued using the human capital approach [95, 96]. This entails that the value to the society of productivity loss is measured as the present value of lost time according to the market wage, including payroll tax. This tax in Sweden was of 31.42% in 2016. Unit prices are presented in Supplementary Appendix to paper II [97].

## 5.2 COST OF LOW BACK PAIN (PAPER I)

The burden of LBP was estimated using a prevalence-based bottom-up approach. This entails multiplying the number of incident cases within a defined period of time with the corresponding cost. In this study, burden was calculated for *LBP episodes*, i.e. time periods of consecutive events close in time, all related to LBP. A patient could have more than one LBP related episode within the study.

For the purposes of this study, an LBP episode begins with a healthcare contact or the start of a work absence period explicitly related to LBP (identified by ICD-10 codes or by being a lumbar spine surgery registered in Swespine). The episode continued until six months has elapsed without a LBP related healthcare contact or work absence, or if the patient dies (six months are commonly used as sign of symptoms resolving) [98]. The end date of an episode was set to the date of the last observed LBP contact or day of work absence. This means that the start of an episode is always preceded by the absence of LBP related healthcare resource consumption for at least 6 months. This is commonly called a *wash-out period*.

Although calculations were made for episodes starting in 2008 and onwards, episodes starting in 2011 were the basis for primary results. The year 2012 was not included, although the data set extracted covered this year, in order to ensure that episodes with long spells of indirect costs were not censored.

In an additional analysis, all healthcare resource use and work loss, considered LBP related or not, were summarised per month during the 24 months before and 24 months after the start of the first observed LBP episode. Only patients with follow up data for the 24 months before and after episode start were included in this analysis.

The following healthcare visits occurring during an LBP episode were included in the cost calculations: general practitioner (GP), other physicians, nurse, physiotherapist, chiropractic, psychologist and other healthcare staff. Outpatient visits and inpatient care counted and costed if they had a registered LBP related ICD-10 code. However, some types of healthcare contacts had no ICD codes or very poor answer ratios. In these cases, the contact was considered to be LBP related if it occurred within an LBP episode. This applied primarily to visits to physical therapists, which are rarely assigned a diagnosis, and other outpatient visits (e.g. assistant nurse, dietician) and hospitalisations without diagnosis code registered. When these visits did have an ICD-code that was not LBP-related, the visits were not included even if it fell within an LBP-episode.

Pharmaceuticals in the analyses were pain medication (ATC codes N02A\* and N02B\*), depression medications (ATC N06\*), muscle relaxants (ATC M03\*) and anti-inflammatory

(ATC M01\*), with asterisk signifying that all sub-codes were included. Because the drug prescription register does not contain diagnosis codes it is not possible to determine the underlying cause for prescribing a drug. All drugs with the above ATC codes prescribed within an LBP episode were therefore included in the calculations. It follows that drug prescriptions did not impact LBP-episode length, such as by starting an episode or prolonging an existing one.

Indirect costs were measured in terms of losses to paid productivity. Absence from work was assumed to be LBP related if it had an explicit LBP related ICD code (as defined above), or if it had any other code and the work absence period was on-going or started during an LBP episode. Two issues with the data needed resolution. First, since data on the proportion of a persons' working time that was covered by a sick benefit during the initial sick-pay period (i.e. the first 14 days paid by employer/employee) were not available, patients were assumed to be on full-time sick leave/early retirement during this period. Second, overlap between sick leave benefit and early retirement had to be adjusted for.

Changes in the social security system and other structural changes have major impact on the use of social benefits [99]. Therefore, a control group consisting of aggregated data from the total Swedish population [100] was included as a reference.

### **5.3 ECONOMIC MODEL (PAPER II)**

The aim of the model is to simulate how patients move both between different health states and between different parts of the healthcare system and capture costs and quality of life. The study took a societal perspective, i.e. included both healthcare resource use (e.g. visits to physician and inpatient care) and indirect costs in terms of productivity loss). Health effects were measured using QALYs and life years.

The model is run using first-order Monte Carlo simulation (individual state transition model). One reason for choosing an individual level simulation technique instead of Markov cohort simulation was due to the large number of states required to accurately depict the treatment pathway and to capture how transition probabilities are affected by dynamic patient characteristics (see chapter 2.2). Its structure is shown in Figure 5.

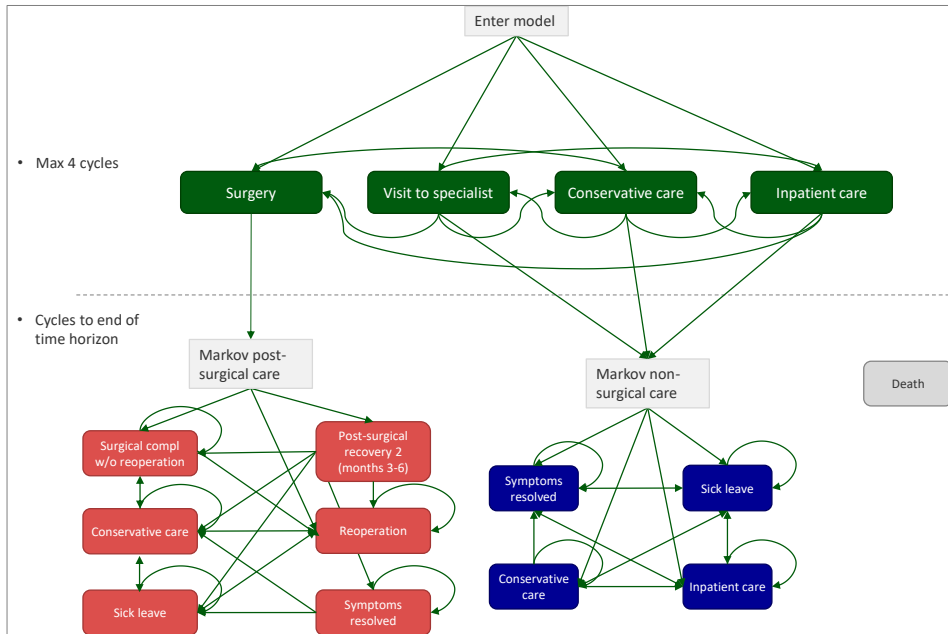


Figure 5: Model outline Model structure. Patient enters the model at the top, to start in a pathway tree of max four cycles, where patient can go between visit to specialist, conservative care, and inpatient care. If patient enters surgery, he goes into Markov post-surgical care (MPSC). Otherwise, patient enters Markov non-surgical care (MNSC) or dies at any stage in the model.

A patient starts the model at the time of first clinical presentation—the *index point*—of the LBP condition. This is often a visit to primary care physician. After the index point, a patient moves through a decision tree for a maximum of four three-month cycles, totalling at most 12 months. During this period, the patient has a chance of receiving conservative care (defined as all outpatient non-surgical care such as physiotherapy), being referred to an orthopaedic or neurosurgical specialist, having spine surgery, or being hospitalized due to the LBP-condition without having surgery. The clinical pathways included in this model were based on the opinion of Swedish physicians, but also by tracking and analysing the observed resource use in the registry data.

If no surgery has been performed during the first 12 months after the index point, the patient moves into the Markov Non-Surgical Care (MNSC) sub-model. Patients can enter MNSC in any of the following four states; symptoms resolved, sick leave, conservative care, and inpatient care. Inpatient care includes surgical treatments not captured within 12 months after the index point.

Lumbar spine surgery was the only orthopaedic treatment included in this analysis. Patients who have undergone surgery within the first 12 months move into the Markov Post-Surgical Care (MPSC) sub-model. In MPSC, patients have probabilities to go to re-operation, surgical complication, or post-surgical recovery, and later into conservative care, sick leave, and symptoms resolved. If a patient dies while in MNSC or MPSC, she moves into the absorbing

death state. A separate Markov model for death (MD) was included for completeness to capture all deaths within the decision tree. The MD model includes only a death state.

Rulebooks were written for how to assign a patient to a given state in the decision tree. The rulebooks both had a set of patient characteristics determining to which state a patient should be sent. Also, it has a strict hierarchy so that if a patient fulfils conditions for two states in the same cycle, the patient was assigned the state higher in the hierarchy. For details, see [97] and its supplementary material.

The probabilities of moving between health states in each cycle were mainly derived from own calculations based on the underlying research database. For the state *symptoms resolved*, mortality was assumed equal to that of the age- and gender-matched general population, based on publicly available data from Statistics Sweden.

QoL estimates for all various health states in the model were not available in the research database, except for patients having surgery. QoL data for non-operated patients was derived from Burström et al. [101], who estimated EQ-5D index values in the general Swedish population and by diseases such as diabetes or depression.

The aim of the simulation was to follow patients from first presentation of symptoms. Therefore, patients were only included if the initial visit was in primary care, and if it was the first visit for LBP in 2 years preceding the index-point.

To analyse the impact of the patient's characteristics, 11 categorical covariates were used: female (yes/no), age, comorbidity, diagnosis group (disc herniation, spondylolisthesis, degenerative disc disease, spinal stenosis, lumbar pain, other), income, born in Sweden (yes/no), and education level (1–7, where 7 is the highest level). Comorbidity was estimated by calculating the Elixhauser comorbidity index [102].

In the simulation, age was time-dependent, while the other covariates were defined at the end of the decision tree and beginning of Markov microsimulation. For the estimation of transition probabilities, effects of covariates were taken into account by adjusting the scale parameter using the coefficients estimated in the Weibull regression. For costs and QoL, ordinary least square regressions were used.

To control for costs that would have been present even if a patient would not have LBP, the model included control groups on costs. This was based on literature. For outpatient visits and inpatient care a control group was derived from aggregated data available in the literature [9]. These aggregated data were indexed to 2016 price level using the latest published consumer price index from Statistics Sweden. The control group for the use of pharmaceuticals was derived from a publicly available report of the National Board of Health and Welfare [103]. For indirect costs, a control group was derived from the general population using official data on sick leave and early retirement from the Social Security Agency. The average control costs were deducted for each cycle and patient in the model

simulation and was assumed to be the same for all cycles. Productivity control cost was deducted for as long as the patient was of working age.

QALYs lost due to LBP was calculated as the difference in QALYs, assuming that QoL is equal to the age- and gender-matched population of the estimated QALYs using the QoL data described above. Estimates of QoL in the Swedish general population were collected from literature [101].

Intangible costs are sometimes considered in studies in the field of health economics, in the context of quantifying the health benefit of certain medical treatment or the strain a disease causes on the quality-of-life of those affected. Several approaches exist to calculate the intangible cost of lost QALYs, including valuing a QALY lost compared with the general population using an assumed WTP threshold [16]. Calculating the intangible cost of a lost QALY thus requires an assumption on the value of life, as no standardized value exists for the monetary value of a QALY. The WTP for a QALY differs among other things on disease severity, where the society is willing to pay more for patients facing serious conditions. The WTP of a QALY derived from decisions made by the Swedish Dental and Pharmaceutical Benefits Agency (TLV) for outpatient drugs was in the interval €79–€135,600 during 2005–2011 [104]. For the base case calculations, an estimate of €70,000 was used as the valuation of a QALY, with lower and higher values used in sensitivity analysis.

The total societal burden was calculated as the sum of direct costs (outpatient visits, inpatient care, and pharmaceuticals), indirect costs (productivity loss), and the intangible value of lost QALYs.

#### **5.4 COST-EFFECTIVENESS OF TOTAL DISC REPLACEMENT (PAPER III)**

In this randomized controlled trial (RCT), 173 patients were randomized to receive either total disc replacement (TDR) or multidisciplinary rehabilitation (MDR). Inclusion criteria were, among others, LBP with duration of more than one year and degenerative changes in lumbosacral intervertebral discs. Data were recorded on follow-up consultations at baseline, at 6 weeks, and at 3, 6, 12, and 24 months after treatment. For further details on the patient inclusion criteria and methods, see the clinical counterpart to this paper [105].

Patients with TDR received disc prosthesis, in the lumbar spine in one or two lower vertebral levels. Patients in the MDR group attended treatment groups based on a model described by Brox et al. [106]. The program, in outpatient setting combining exercises and cognitive behavioural therapy (CBT), was directed by a team of physiotherapists and specialists in physical medicine and rehabilitation. It lasted for approximately 60 hours during 3–5 weeks.

Resource use was collected and valued, using a societal perspective. Cost included the index treatment, other hospital care, primary care, patients' private costs, and costs due to loss of production both for the patient and their relatives. Actual costs were assigned to patients regardless of their randomized group, so patients who were randomized to receive MDR but

crossed over and underwent operation after having had MDR were assigned costs for both treatments.

For TDR, the resource use multiplied by unit costs, and incorporating spare capacity when appropriate, summarized the cost for each index treatment. Cost components included the prosthesis, operation room time, wake-up services, postoperative stay in hospital, and postoperative radiograph.

For MDR, a top-down approach was needed. The total cost of a spine clinic was estimated, and then how much of the clinic's costs were associated with MDR was determined. A consequence of this approach is that the costs are the same for all patients. Spare capacity was included. A premium of 12% was added to common costs based on data from previous estimates of the cost weights for the Norwegian DRG system. Planned and unplanned readmissions, including outpatient visits and reoperations, were registered in electronic patient administrative systems. Patients who underwent surgery received one mandatory consultation with a radiograph 6 weeks after surgery. Patients in the MDR group were offered 4 follow-up consultations at 6 weeks and at 3, 6, and 12 months, and costs were assigned if accepted.

Unplanned visits to general practitioners, physiotherapists, or other practitioners in the public health service were recorded in a cost diary kept by the patient [107], as well as the use of medication (both prescribed and over the counter), contact with practitioners outside the public health service, and other costs. Costs for relatives were included when possible.

Productivity loss is normally a major part of the costs. The human capital approach was used to estimate the costs related to days each patient spent out of work due to low back pain. Costs related to production losses were calculated as the number of days out of work multiplied by the average wage. These were adjusted for part-time sick leave as appropriate. Income before taxes was used for patients and after taxes for relatives when calculating costs related to work loss as instructed by the Norwegian Medicines Agency [108].

To measure treatment effects, the EQ-5D was used in the main analysis and SF-6D for comparison [15]. Both costs and effects were measured at baseline, at 6 weeks, and at 3, 6, 12, and 24 months after treatment, thus enabling us to calculate quality-adjusted life years.

To derive a confidence interval (CI) for the incremental cost-effectiveness ratio, 10,000 nonparametric bootstraps were simulated. These were plotted in a cost-effectiveness plane to illustrate the uncertainty in the ICER. Also, a cost-effectiveness acceptability curve (CEAC) was graphed. The CEAC shows how likely a treatment is considered cost-effective given different levels of willingness to pay (WTP) for a gain of one QALY. As a baseline, the value of NOK 500,000 or €74,600 was used [109]. The intention-to-treat (ITT) method was used, and per-protocol analysis (PP) was presented in the sensitivity analysis.

Missing data were handled by multiple imputations, imputing 5 data sets as commonly recommended [110–112]. Student t tests and corresponding 95% CIs were used to analyse

differences in cost and utility. Two-sided P-values < 0.05 were regarded as significant. Given the short follow-up period, neither treatment effects nor costs were discounted.

Sensitivity was tested by a) applying different utility measures (EQ-5D and SF-6D) (see for example [113]), b) using PP instead of ITT, c) not applying the method of multiple imputations, d) applying different estimates for the loss of production, and e) excluding the cost of care provided by relatives from calculations.

## **5.5 COST-EFFECTIVENESS OF FUSION IN DECOMPRESSION SURGERY (PAPER IV)**

We conducted a multicentre, open-label trial in which patients who had lumbar spinal stenosis, with or without degenerative spondylolisthesis (DS), were randomly assigned, in a 1:1 ratio, to undergo either decompression surgery plus fusion surgery (D+F) or decompression surgery alone (D). Patients between 50 and 80 years of age with lumbar spinal stenosis were recruited, subject to further technical inclusion criteria.

Simple randomization was performed with the use of a web-based system that enabled computer-generated random treatment assignment. Randomization was stratified according to the presence or absence of DS.

Outcomes of this trial were measured with the use of patient-reported data obtained from validated questionnaires. Patients were included in the National Swedish Register for Spine Surgery (Swespine) database. Swespine collected data before surgery and 2 and 5 years after surgery, with periodic reminders to patients when necessary.

The primary outcome was the score on the Oswestry Disability Index (ODI), a standard for measuring degree of disability and estimating quality of life in persons with low back pain. EQ-5D was among secondary outcomes collected.

Additional data for the health economic evaluation were collected by means of special questionnaires that were unrelated to the Swespine. The questionnaires were sent before surgery and 6 months, 1 year, and 2 years after surgery. Data on direct operation costs were obtained from one clinic, Stockholm Spine Center, and used as a proxy for all participating clinics. Data on direct and indirect patient costs included the number of visits to health care personnel, use of sick leave, participation in the work force, use of pharmaceutical agents, length of hospitalizations, personal out-of-pocket expenses, and number of days that family members assisted the patient. In accordance with the trial protocol, data on patient costs were not collected after 2 years.

Differences between the two treatment groups were analysed with the use of Student's t-test using per protocol analysis. In addition, we calculated relative risks and 95% confidence intervals by comparing outcomes in the two groups. The analysis was performed both with and without stratification according to the presence or absence of preoperative DS. Less than 2% of patients had missing outcome data for each of the variables.

As in paper III, we used multiple imputation to create five estimates of missing data in the health economic evaluation, including values for age, sex, and scores on the visual-analogue scales for back pain and leg pain, the ODI, and the EQ-5D. Values for the health economic evaluation were imputed for 30% of patients at the 6-month follow-up, 33% at the 1-year follow-up, and 14% at the 2-year follow-up. Calculations of standard deviation and error were adjusted to account for the increased size of the data set.



## 6 RESULTS

### 6.1 COST OF LOW BACK PAIN (PAPER I)

In order to assess the economic burden of LBP, all related episodes were identified over a four-year period. These made up a total of 167,460 LBP episodes in 134,309 individuals. The mean age at episode start was 52 years and 59% were women. The mean total cost for an LBP episode was estimated at €2,758. Of total cost, 66% was related to indirect costs (sick leave and early retirement). The largest healthcare cost category was visits to physician, accounting for 10% of total costs. The smallest cost category was other outpatient visits, i.e. visits other than to physician and physiotherapist, which accounted for 1% of the total costs. The distribution of costs was highly skewed to the left, indicating that most of costs emerged from a minority of the patients. This is manifested in the fact that the median costs are markedly lower than the mean.

Figure 6 presents direct, indirect and total costs per month for 24 months prior and 24 months after start of the first observed LBP episode. These numbers include all healthcare resource use and work loss whether LBP-related or not. The figure also shows the indirect costs of the general population. Costs followed the LBP episode start, with a marked short-term increase of costs at the first month after episode start. In the second month after episode start, cost levels were noticeably lower compared to the first month. Following the second month, costs continued to gradually decrease. At the end of the two-year period, costs had plateaued at a higher level than prior to episode start.

Indirect costs decreased during the years leading up to episode start, mirroring the trend in the general population. Changes in the social security system (e.g. the so-called rehabilitation chain implemented in 2008) and/or structural changes in the Swedish economy have affected the use of sick leave benefits.

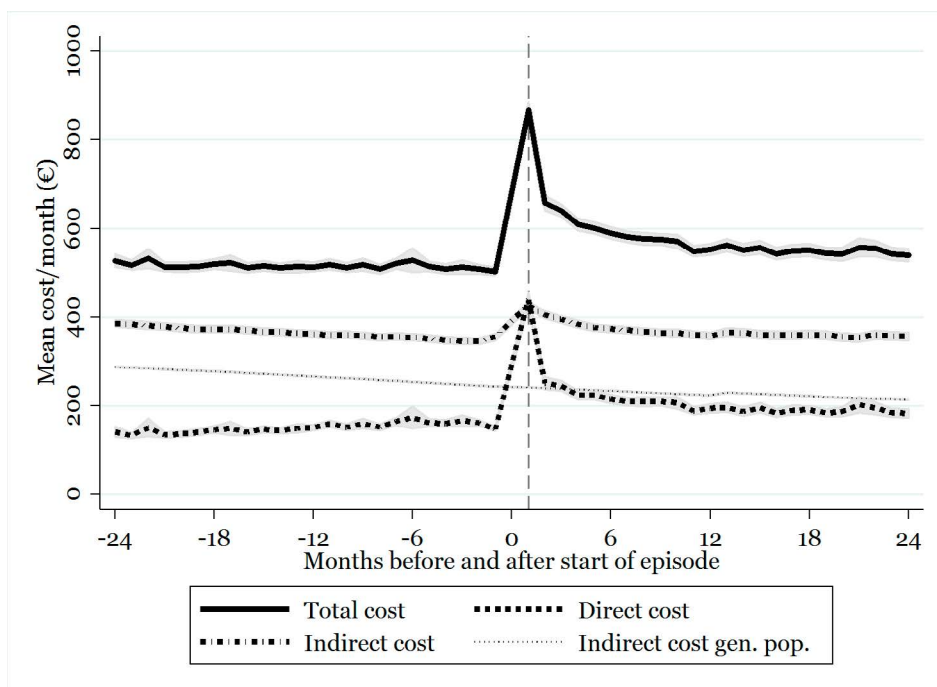


Figure 6: Mean indirect, direct and total cost per patient and month during 24 months before and 24 months after the start of the first LBP episode. The dotted line shows the indirect cost per month in the total Swedish population. Includes both LBP related and non-LBP related costs. Shaded areas show 95% confidence intervals of the means.

If the LBP population in VGR in terms of incidence and demographic composition is representative for the whole of Sweden, the number of LBP episodes that started in 2011 in Sweden was calculated at 293,000. Using this, the societal cost amounts to €739 million, or €78 per capita (Table 3). 65% of the total cost could be related to work absence.

Table 3: Mean national cost (million €) of LBP episodes started in 2011 in Sweden.

Category	Million EUR (€ million)	Per capita (€)
Pharmaceuticals	11	1
LBP surgery	72	8
Non-surgical related inpatient care	126	13
Medical visits	95	10
Physical therapy	25	3
<b>Direct costs</b>	<b>258</b>	<b>27</b>
Work absence - sick leave	330	35
Work absence - early retirement	151	16
<b>Indirect costs</b>	<b>481</b>	<b>51</b>
<b>Total costs</b>	<b>739</b>	<b>78</b>

The data is presented graphically below

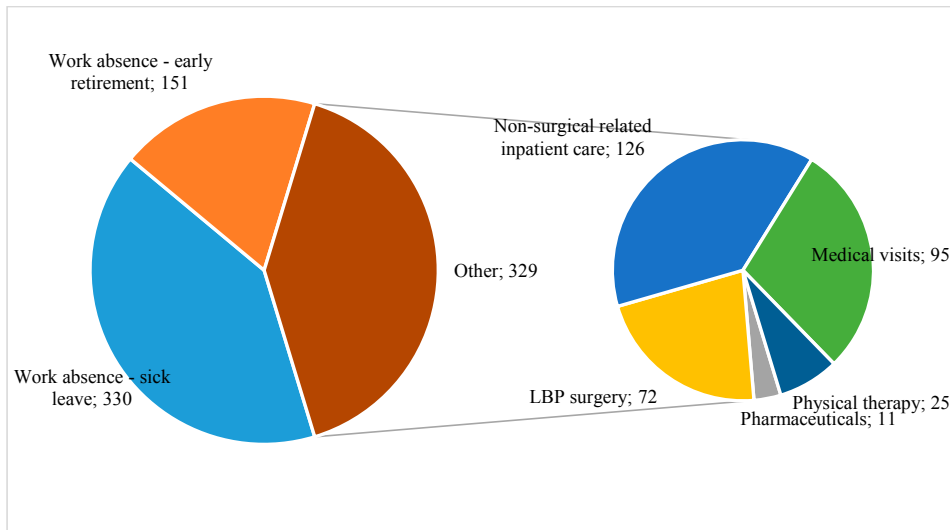
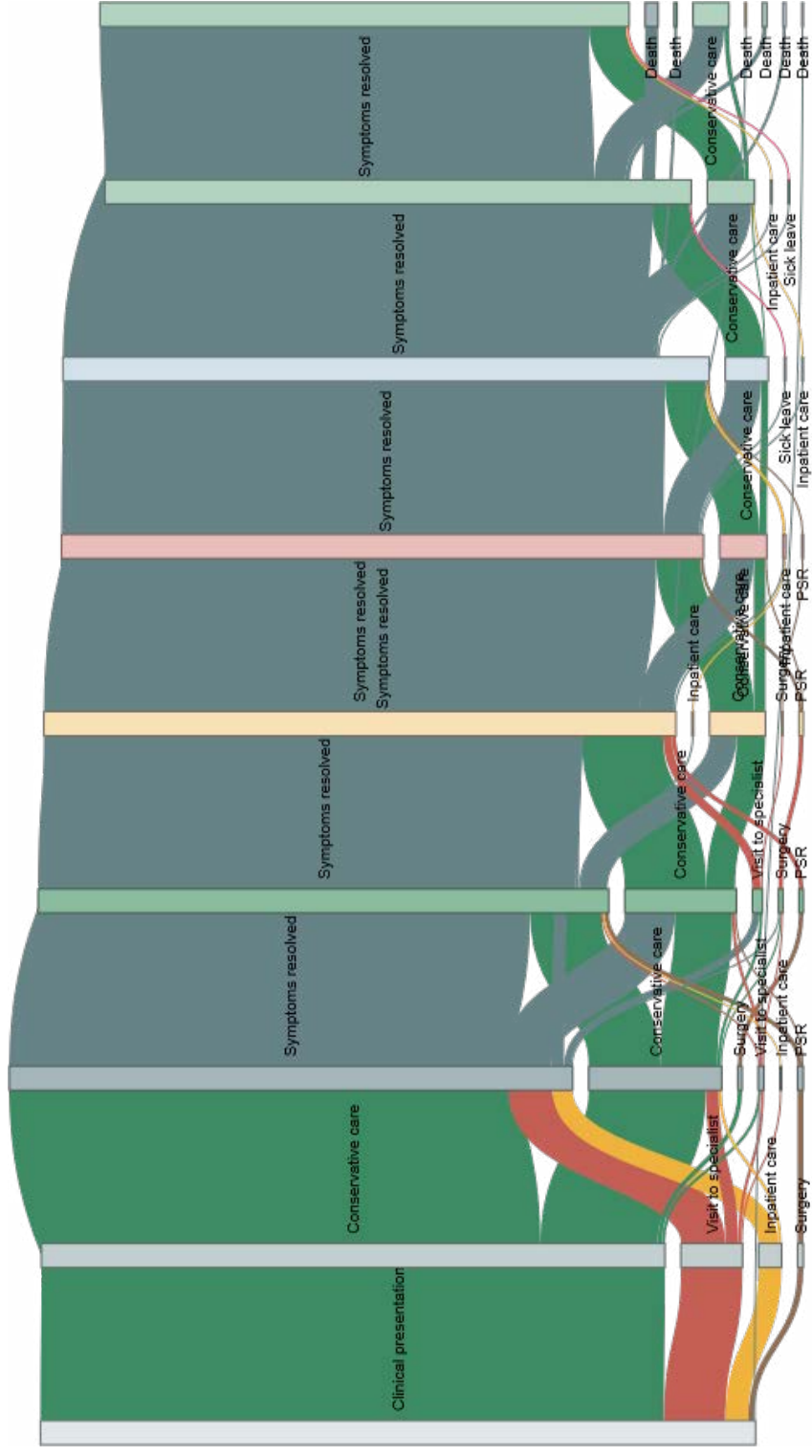


Figure 7: Breakdown of costs, million euros (same data as in Table 3.

## 6.2 ECONOMIC MODEL (PAPER II)

In total, 154,209 patients were identified in the registry data and included for analysis. Most patients (57%) were women, born in Sweden (74%), and the mean age at clinical presentation was 50 years. The mean number of comorbidities according to Elixhauser index was 0.7.

Within 3 months after clinical presentation, 93% consume conservative care. An additional 6% visit specialists, potentially for surgical evaluation. Twelve months after clinical presentation, 90.2% have seen their symptoms resolved, 8.8% have received conservative care, 0.5% have undergone surgery or received post-surgical care, and 0.3% have died. This is illustrated in Figure 8. Other health states have a low proportion of patients.



Mean lifetime costs are, on average, €47,452, as presented Table 4. Pharmaceuticals are the smallest single cost category, with 9% of the total costs; inpatient visits constitute 20% of the costs, outpatient visits 14%, and indirect costs 57%.

*Table 4: Average discounted cost averaged over the whole patient population.*

<b>Costs</b>	<b>Mean</b>	<b>Percent of total</b>
<b>Pharmaceuticals</b>	4,431	9,3%
<b>Inpatient visits</b>	9,311	19,6%
<b>Outpatient visits</b>	6,616	13,9%
<b>Indirect costs</b>	27,095	57,1%
<b>Total costs</b>	47,452	100%

Quality-of-life Mean QALYs per patient accrued from the point of clinical presentation were estimated at 14.0, and the number of life years at 18.0 per patient, as shown in Table 5. The burden of LBP in terms of lost QALYs over the lifetime of the patient as compared with the age and gender matched Swedish population was estimated at 2.7 per patient.

The total lifetime cost of all patients coming to clinical presentation in one year in Sweden was estimated at €8.8bn. QALYs lost in the same population were estimated at 505,407.

*Table 5: Mean QALYs & life years in the model*

<b>QALYs accrued from clinical presentation</b>	13.97
<b>QALYs lost</b>	2.7

Valuing this at €70,000 per QALY yields a burden of lost QALYs of €35.3bn. The total lifetime costs added together with the intangible cost of lost QALYs yields a total societal burden in Sweden of €44.1bn in patients coming to clinical presentation in 1 year.

### **6.3 COST-EFFECTIVENESS OF TOTAL DISC (PAPER III)**

Full cost data were provided for 84% of the patients (144 of 173). Baseline characteristics were similar between groups, presented in detail in the clinical paper [105]. In all, 13% of resource use data during follow-up and 8.3% of utility scores were missing between baseline and 24 months. Five patients crossed over from MDR and underwent TDR. Nine patients randomized to surgery decided not to undergo surgery. Five patients in the TDR group underwent re-operation.

A significant difference in EQ-5D utilities in favour of TDR was found at all follow-ups except at 6 weeks. After 2 years, the mean total improvement in QALYs (standard deviation) was 1.29 (0.53) in the TDR group and 0.95 (0.52) in the MDR group, a significant difference of 0.34 QALY (95% CI, 0.18–0.50). This is shown in Figure 9.

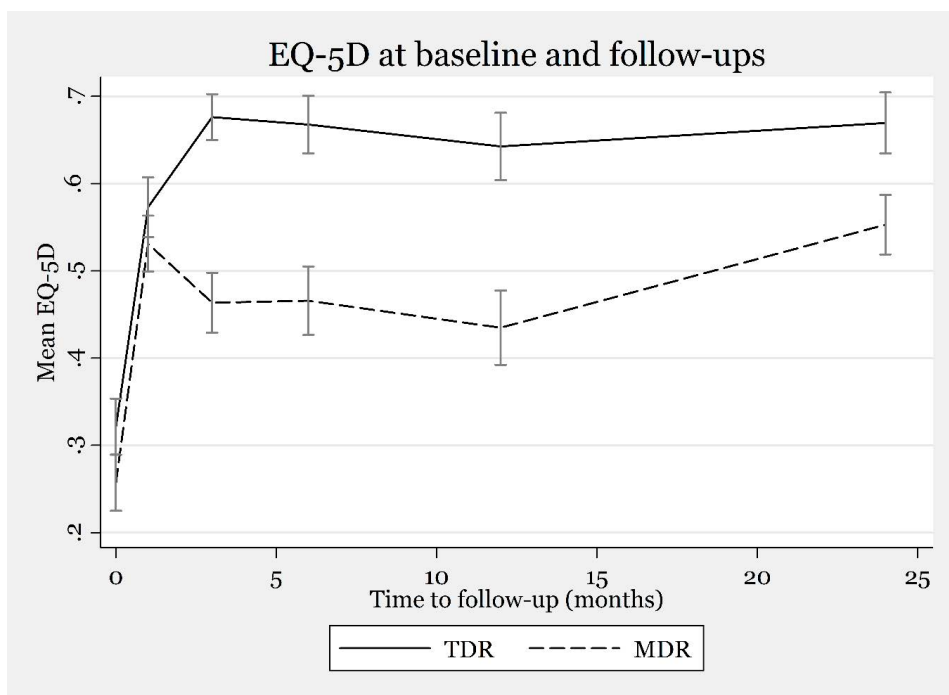


Figure 9: EQ-5D at baseline and follow-ups. Utilities (mean  $\pm$  2SE) at time to follow-up derived from EQ-5D scoring. Significant difference in favour of TDR was found at all times of follow-up, except at 6 weeks (independent 2-sided t-test).

The mean cost of the index operations was estimated at €10,846 for TDR and €5977 per patient with MDR.

For other cost categories, costs were somewhat different but not the difference was not statistically significant. This applies to the follow-up costs (cost of visits to general practitioners, physical therapists, and other health care professionals, as well as medication use). The same goes for production loss which entailed both personal costs and the work loss of relatives.

The total costs included index treatment and costs during the 2-year follow-up. The total cost was €87,622 (58,351) and €74,116 (58,237) in the TDR and MDR groups, respectively. The difference of €13,505 was not significant ( $P = 0.14$ ). This is detailed in Table 6.

Table 6: Summary of initial treatment and follow-up costs and effect after 2 years follow-up.

	TDR		MDR		Mean difference	CI	p-value
	Mean	SD	Mean	SD			
<b>QALY EQ-5D</b>	1.29	0.53	0.95	0.52	0.34	(0.18 to 0.5)	<0.001
<b>QALY SF-56D</b>	1.33	0.21	1.22	0.18	0.11	(0.05 to 0.17)	0.001
<b>Index treatment (€)</b>	10,846	1,846	5,977	1,229	4,869	(4,396 to 5,340)	<0.001
<b>Follow-up cost (€)</b>	8,381	10,580	6,609	12,474	1,772	(-1,712 to 5,251)	0.35

<b>Loss of production (€)</b>	68,395	54,227	61,528	54,633	6,865	(-9,518 to 23,250)	0.43
<b>Total cost (€)</b>	87,622	58,351	74,116	58,237	13,506	(-4,440 to 31,452)	0.14

Using EQ-5D as the measure of quality of life, the mean ICER in the TDR group was €39,748/ QALY (95% CI €15,990 to €65,645). We calculated 10,000 bootstrap estimates of the ICER, of which 2000 were plotted in the cost-effectiveness plane, illustrating the uncertainty of the ICER estimates (Figure 10 ).

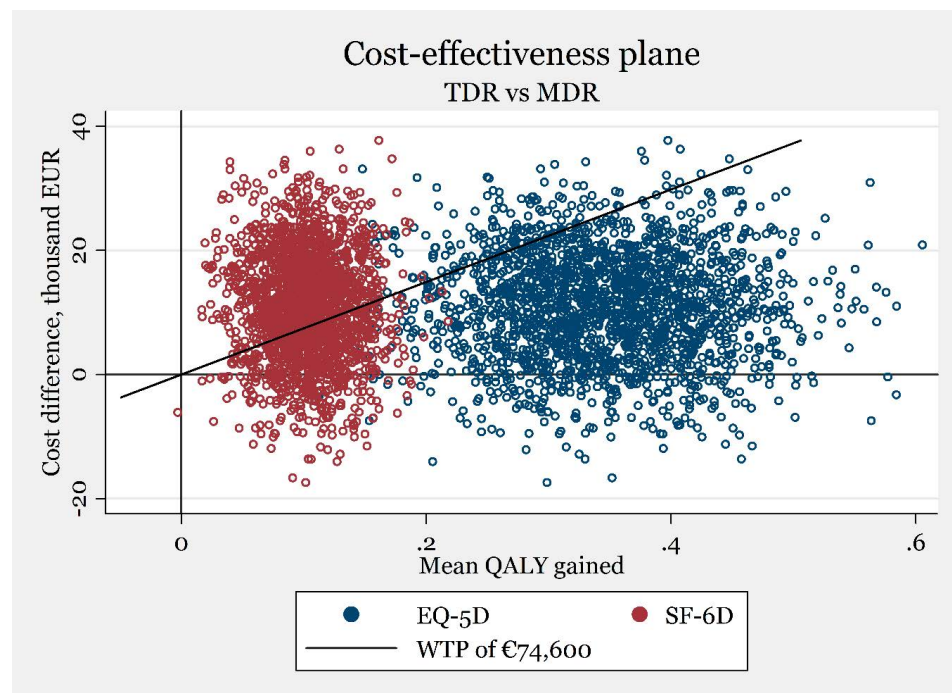


Figure 10: Cost-effectiveness plane. Plot of 2,000 bootstrap replications of ICER in a cost-effect plane. For calculations, 10,000 replications were made but these are reduced here for illustrative purposes. The plot shows that on average, little cost difference seems to be between TDR and MDR, while TDR yields higher QALY increase. The black line is the willingness-to-pay for given QALY gain. Dots falling below that line and the horizontal red one are cost-effective; dots falling below the horizontal red line are cost-saving.

If decision makers and relevant stakeholders are willing to pay €74,600 (NOK 500,000) for one QALY [109], the chance of TDR being cost-effective from a societal perspective was approximately 90% using EQ-5D. This is illustrated in the cost-effectiveness acceptability curve in Figure 11. When using a willingness-to-pay limit of three times the gross domestic product per capita (\$233,000 in 2011 in Norway) as recommended by the World Health Organization, TDR was cost-effective irrespective of utility measure used Figure 11).

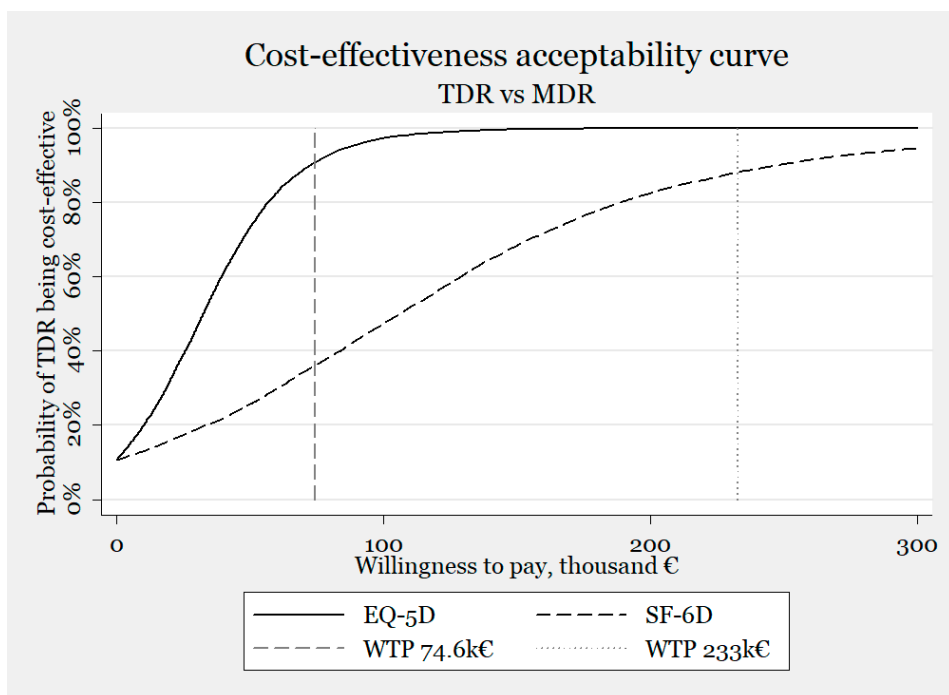


Figure 11: Cost-effectiveness acceptability curve. The vertical line shows a commonly used thresholds for maximum willingness to pay (WTP) in Norwegian setting. The curve represents the probability that the cost-effectiveness of TDR is lower than the corresponding WTP.

### 6.3.1 Sensitivity analyses

Several sensitivity analyses were done to gauge the results' response to differences in assumptions. These are presented in Table 7.

All analyses were performed using both EQ-5D and SF-6D. Using SF-6D with other base-case assumptions, the improvement in the TDR group above MDR was 0.11 QALY (95% CI, 0.05–0.17), somewhat less than the gain of 0.34 QALY (95% CI, 0.18–0.50) using EQ-5D was used. The ICER in the TDR group was €128,328/QALY (95% CI €51,329 to €219,907), and the chance of TDR being cost-effective from a societal perspective was approximately 40%, that is not cost-effective (Figure 11).

Using per-protocol analysis instead of ITT analysis indicated that TDR was not cost-effective, irrespective of the use of EQ-5D or SF-6D.

Multiple imputation is the method of inserting a distribution of values into missing fields. This is done to avoid excluding patients with a few missing values and to avoid bias. Five data sets were created where missing values were replaced with different imputed values, reflecting the uncertainty around the missing value. When these methods were not used, a considerable number of observations were lost. ICER rose, making TDR not cost-effective.



As productivity losses by patients and their relatives constituted a high cost component, we arbitrarily raised and lowered the estimated cost per day by 30%. This only had a moderate effect on cost-effectiveness and did not alter the conclusions.

Similarly, days spent by relatives were excluded to see how this changed the results. As patients undergoing surgery required more care by their relatives, excluding these costs decreased the ICER and thus increased the likelihood of TDR being cost-effective.

Table 7: Sensitivity analyses

Variable/method	Description	Mean cost difference (€)	Mean EQ-5D gain	Mean SF-36 gain	ICER EQ-5D (€/QALY)	ICER SF-6D (€/QALY)	Comments
<b>Base case</b>							
<b>Per-protocol analysis</b>	Values as presented in results. Intention to treat was used as base case, this analysis used per-protocol analysis, i.e. patients who crossed over from MDR to TDR were analysed as a part of TDR group.	13,506 30,558	0.340 0.353	0.105 0.092	39,748 86,669	128,328 331,316	Using per-protocol analysis indicated that TDR is not cost-effective, regardless of outcome measure.
<b>Multiple imputation</b>	Multiple imputations were used in the base case to stand in for missing values. Here, where values necessary for analysis were missing, the patient was dropped from analysis.	26,259	0.191	0.093	93,818	281,545	When not using multiple imputations, 78 patients were included in the EQ-5D calculations and 54 in SF-6D calculations (of total 172). The dropout and missingness of data cannot be assumed to be at random. Of these 172, 144 did stay within the study, 28 dropped out at some point.
<b>Loss of production</b>	As a base case, the loss of production was assumed to be the average income per capita. Here, the value was arbitrarily decreased and increased with 30%.	11,446 / 15,566	0.340	0.105	33,686 to 45,810	108,757 to 147,898	Loss of production is a big factor in the total cost of follow-up. However, as loss of production is distributed relatively evenly across treatment arms, changing the cost of each lost day does not affect the result much.
<b>Days spent by relatives</b>	As a base case, days spent by relatives were included. A sensitivity analysis was made where these costs were not taken into account.	8,173	0.340	0.105	24,054	77,660	As TDR patients required more care by their relatives, excluding the associated costs increased the likelihood of the surgery being cost-effective.

**6.4 COST-EFFECTIVENESS OF FUSION IN DECOMPRESSION SURGERY (PAPER IV)**

From October 2006 through June 2012, a total of 247 patients from seven Swedish hospitals were enrolled in the trial. No significant differences between the two treatment groups in any of the preoperative variables, including general health. A total of 123 patients were assigned to the fusion group, and 10 of those patients did not receive the assigned treatment; 124 patients were assigned to the decompression-alone group, and 4 of those patients did not receive the assigned treatment. Therefore, 113 patients underwent decompression surgery plus fusion surgery and 120 underwent decompression surgery alone. Five patients were lost to follow-up. Therefore, the per-protocol analysis included 228 patients (111 in the fusion group and 117 in the decompression-alone group)

No significant difference between the two treatment groups in the primary outcome; the mean score on the ODI at 2 years was 27 in the fusion group and 24 in the decompression alone group ( $P = 0.24$ ).

This result—a lack of difference between groups—was evident across variables and group specifications, the 6-minute walking test being an example of the former and pre-existing degenerative spondylolisthesis of the latter. Also, ITT analysis instead of PP showed no difference between groups.

All but one patient consented to participate in the health economic evaluation, with data on resource use at 2 years available for 213 patients (92%). EQ-5D values at baseline were 0,37 for D and 0,39 for D+F. After the operations, QoL jumped to 0,66 and stayed there at the 2-year follow-up. At no point were QoL statistically different. This is shown in Figure 12. Similarly, ODI was not different between groups at any time [114].

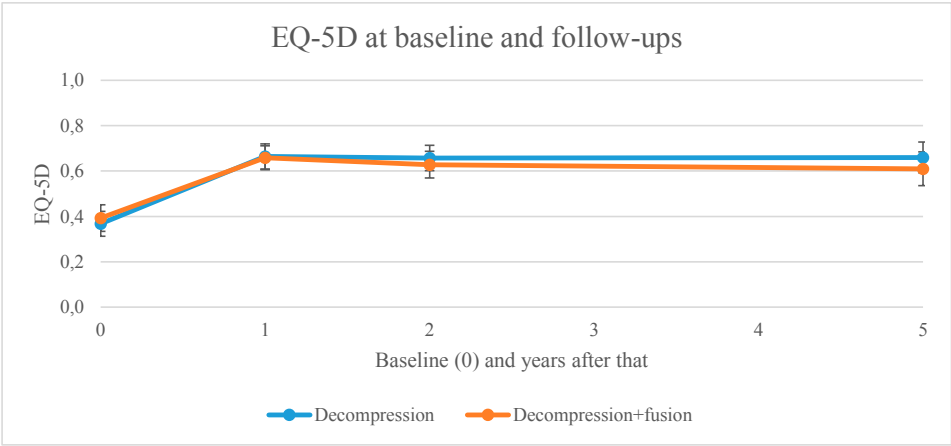


Figure 12: *Quality of life (mean  $\pm$  2SE) at baseline and follow-ups. Difference between groups was not statistically significant at any point. See data in Table 8.*

Indeed, among the 153 patients who were enrolled early enough in the trial to have potentially completed 5 years of follow-up, 7 had died, 1 had had a major stroke, and 1 had

severe dementia; the remaining 144 patients were eligible for the 5-year follow-up assessment. Of those patients, 138 (96%) provided information on outcomes. Again, there were no significant differences between the fusion group and the decompression-alone group in any of the seven patient-reported outcome measures—including EQ-5D—and the results were similar among patients with and those without spondylolisthesis (see supplementary material to [114]).

Table 8: EQ-5D at baseline and follow-ups. Same data as in Figure 12.

	Decompression				Decompression+fusion			
	EQ-5D	SD	SE	N	EQ-5D	SD	SE	N
<b>Baseline</b>	0,37	0,30	0,05	119	0,39	0,31	0,06	113
<b>1 year</b>	0,66	0,30	0,06	119	0,66	0,28	0,05	113
<b>2 years</b>	0,66	0,30	0,06	119	0,63	0,31	0,06	113
<b>5 years</b>	0,66	0,29	0,07	73	0,61	0,30	0,07	65

Resource use is shown in Table 9. The mean direct costs of each procedure (mainly hospital costs, including surgery) were \$6,800 higher in the D+F group, because of the additional operating time, extended hospitalization, and cost of the implant. However, indirect costs were similar in the two treatment groups.

Analyses performed with stratification according to the presence or absence of degenerative spondylolisthesis at baseline resulted in outcomes that were similar to the outcomes in the overall analysis.

Table 9: Resource use

Item	D	D+F	Difference
<b>Perioperative</b>			
<b>Length of stay (days)</b>	4.06 (0.56)	7.34 (0.79)	3.28, p<0.001
<b>Operation cost (SEK)*</b>	44,884	101,332	56,448
<b>Follow-up</b>			
<b>Number of visits to doctors (SE)</b>	1.73 (0.46)	1.29 (0.31)	-0.44, p=0.49
<b>Number of visits to other health care professionals (SE)</b>	21.6 (4.1)	13.0 (3.0)	-8.86, p=0.13
<b>Total days on benefits of any kind (SE)</b>	40.7 (10,9)	61.4 (16,4)	23.7, p=0.35
<b>Still using drugs at 24 months (SE)</b>	33.6% (4.3%)	37.2% (4.5%)	-3.6%, p=0.57

\*Calculated from hospital accounting system. No measure of distribution available.

## 7 DISCUSSION

### 7.1 PAPER-SPECIFIC DISCUSSION

#### 7.1.1 Burden of Low Back Pain, including Lumbar Disc Herniation and Lumbar Spinal Stenosis (common for papers I and II)

Using a representative Swedish region constituting 17% of the total population in the country, an average LBP episode was estimated at 51 days with an average total cost of €2,671. When extrapolating the results to the whole of Sweden, the yearly national societal cost of LBP was estimated at €739 million in all LBP episodes that started during 2011. The trajectory of total costs shows that there is a sharp cost increase at the first month of following the episode start, which decreases markedly from the second month after this point. Importantly, costs were not entirely restored to pre-episode levels during the two years after the episode start. This indicates that LBP has long term consequences on resource use and costs.

The estimated cost per capita of €78 in 2011 in the current paper I can be compared to previous estimates. According to a systematic review of international cost-of-illness studies of LBP, the total cost per capita has ranged from €48 to €2,874. Two Swedish studies were included in this review, which both estimated considerably higher costs per capita compared with our study. Ekman et al. estimated the cost to be €250 per capita in 2016 year prices [9]. In this study, direct costs were similar to our estimate while indirect costs were nearly three times higher. An explanation might be that the rate of sick leave in the whole Sweden was markedly higher around the years 2001–2002, falling from 21 days per individual and year to 7 in 2010 [99].

The direct economic cost of LBP per patient was estimated at €47,500, which amounts to €8.8bn per year in Sweden. When both indirect costs and intangible costs of QALYs lost were added, QALYs, the burden was estimated as €44.1 billion using a WTP of €70,000 per QALY, with lost QALYs representing more than half of the total societal burden.

Most studies on the cost of LBP use a prevalence-based methodology, examining costs incurred during a given time period such as 1 year, regardless of the timing of onset of disease [31]. In our study, we assessed the lifetime costs in patients from first symptoms, which makes it less accurate to compare our estimated costs with other studies. In 2002, Ekman et al.[9] estimated the annual cost of LBP per patient at €20,700 in 2002. On a national level in Sweden, the total cost has previously been estimated at €1,860m in 2001 and €3,346m in persons who were sick-listed for LBP in 1994–1995 [115]. A Swiss study found the direct costs of LBP to be €2.5bn and productivity loss at €4.1bn using the human capital approach. In the US, the indirect costs for LBP on a national level has been estimated at \$19,800m [116] and \$7,400m [117] in 2002 and 2004, respectively. The health-related burden of LBP has been estimated in terms of the DALYs. The Global Burden of Disease estimated the global number of lost DALYs in 2010 to 83 million [4].

Previous studies have indicated that most of the economic burden of LBP is due to indirect costs. Ekman et al. [9] estimated that 85% of the annual cost of LBP were indirect costs and Walker et al. [30] 89%. The lower share of indirect costs in our study might be since we used a control group of people on sick leave and early retirement from the general population, which is more accurate and less likely to overestimate the costs.

#### *7.1.1.1 Indirect costs*

The use of sick leave/early retirement in the total Swedish population decreased over the investigated period. The trajectory of indirect costs before the start of the LBP episodes followed this general trend. However, indirect costs remain on a rather stable level after first month after episode start, while in the general population, the indirect costs continued to decrease. This signals a connection between the cost of LBP on one hand and general economic and structural trends in the society on the other.

#### *7.1.1.2 Modelling approach*

To date, no previous studies have investigated the long-term treatment patterns, costs, and QoL of patients with LBP. The estimation of expected costs and health effects of interventions at specific time point within a broader care pathway is perhaps the most commonly applied economic evaluation to directly inform policy decisions.

Whole disease modelling, with the aim of assessing the lifetime consequences and/or interventions across the entire disease pathway has recently gained more attention. Tappenden et al. [118] developed a methodological framework for whole disease modelling. While most economic analyses are piecewise, i.e. involve estimation of costs and health effects in specific points in a broader treatment pathway, our framework allows multiple evaluations of changes in healthcare services. As changes to a specific part of the care treatment pathway may have downstream effects, it is important to ensure that all possible costs and benefits are incorporated in the analysis.

A wealth of other modelling approaches were available [20]. One would have been to use Markov cohort model. We decided against that approach, mainly because of the need for patient history to inform the transition probabilities and outcomes. Another approach, would have been discrete event simulation [119]. However, not only are discrete event simulations complex to construct and data-hungry, but their complexity and sophistication makes the presentation of assumptions and structure very difficult. Thus, transparency and reproducibility suffers [120].

Modelling requires an assumption of the cycle length which should be decided using the timing of events in the progress of the disease in question, study question, and available data, among other things. Fixed cycle length affects what type of data needs to be collected and forces existing data into unrealistic boxes.

The transition probabilities in the model were based on the analysis of Swedish register data which provide high-quality data on healthcare resource use.

#### *7.1.1.3 Intangible costs*

Measuring intangible costs requires an assumption of the value of life, which makes this a particularly challenging cost to measure. This value differs between countries and disease severity among other things. Thus, there exists several different standards of the value of QALY. In this study, we used a WTP threshold of €70,000, which corresponds to the lowest interval of the Swedish Dental and Pharmaceutical Benefits Agency WTP for outpatient drugs. In reality, the WTP may be much lower for low back pain treatments. We performed a sensitivity analysis using WTP thresholds ranging from €20,000–€100,000. This showed the linear relationship between the valuation of QALYs and the intangible burden on society. Uncertainty around the WTP should not diffuse the main message that in addition to high economic burden, the brunt of the effect is in the non-monetary burden. The WTP in the model could also easily be altered, depending on different assumptions in different countries.

#### *7.1.1.4 Limitations*

These studies are not without limitations. Although the data set is unique in its thoroughness and detail, some factors could not be assessed. First, the calculations on a national level assume that the LBP population in the region of Västra Götaland in terms of incidence and demographics is representative for the whole Sweden. Second, the data lacked some variables that might be of interest. No direct information was available on diagnostic imaging as these are not reported separately in the available data, nor was cost due to durable medical equipment available separately.

We did not have data on sick leaves shorter than 14 days. No data on individual level exists on presenteeism (i.e. reduced work capacity when working) or the inability to perform household work. Therefore, the indirect cost of work absence may be to some extent underestimated.

Further, out-of-pocket costs for over-the-counter drugs are not included. Another variable of interest is paid home help. Fritzell et al. estimated the cost of family support, such as housekeeping, for patients eligible for surgical treatment for LBP, reaching estimates between €13–16,000 over two years (2016 prices) [107]. Although the patients eligible for surgery is a rather small proportion of the total population in our sample, the lack of information in this regard is a potential downward bias in our cost estimates.

Our bottom-up approach relies on coding or context for relating costs to LBP. This might underestimate the costs, due to for example lack of coding, costs falling outside the reach of our data set, and due to secondary effects of LBP on other health problems.

Due to the diffuse nature of LBP, and common inaccuracies in initial diagnoses, a very broad definition of LBP was used.

One possible limitation with data is that we cannot observe if the LBP symptoms truly had disappeared. Since a patient was assumed to have its symptoms resolved based on that he or she did not visit healthcare or was on sick leave due to LBP symptoms, the proportion of patients who have their LBP symptoms resolved may be over-estimated.

### **7.1.2 Cost-Effectiveness of total disc replacement for Low Back Pain (Paper III)**

This paper compared the outcome of total disc replacement—a surgical procedure—with multidisciplinary non-surgical treatment. Both improved quality of life considerably during the first two years. Using EQ-5D, the most commonly used instrument in health economic evaluations, the chance of TDR being cost-effective was 90% using the threshold of €74,600 (NOK 500,000) often used in Norway [108, 109]. However, three of the five sensitivity analyses performed changed the conclusions: using SF-6D instead of EQ-5D, using per protocol analysis instead of ITT analysis, and not using multiple imputations, see Table 7 on page 53.

#### *7.1.2.1 EQ-5D or SF-6D*

Although EQ-5D is the most common assessment used in health economic evaluations, there is no general agreement on which instrument is most appropriate. This would be innocuous if results were always similar. This is however not the case [15, 113, 121].

Not only are the two instruments different in the questions and the possible answers, but the way these are mapped onto a numerical scale differs. EQ-5D uses time trade-off (TTO) while SF-6D standard gamble (SG) [122]. Using SG, people are asked to take a risk while the TTO is riskless. Second, while the TTO method assumes a defined period living in perfect health, no such time frame is introduced in SG. As a result, TTO—and thus EQ-5D—tends to yield lower utilities than SG and SF-6D [123]. This was manifested in the present study, where EQ-5D showed a ceiling effect while SF-6D showed a floor effect [15], and unfortunately the cost-effectiveness of TDR was dependent on the choice of utility index.

However, EQ-5D was used as baseline utility measure as it is most widely used in cost-effectiveness studies. This makes comparisons with other treatment choices easier. In addition, more patients had completed the EQ-5D questionnaire resulting in more complete data with this index, not surprisingly as one of the main design goals of EQ-5D was conciseness to improve completion rates.

#### *7.1.2.2 Treatment of crossovers and missing values*

The results are different when it comes to how crossovers are analysed. Arguably, patients who do not follow their randomized treatment are in one way or another different from the rest of their treatment group. Some of these differences can be observed, but unobserved differences cannot be ruled out either. For this reason, ITT analysis is considered the gold standard in health economic evaluations [23].



Moreover, questions in health economics often are about what policy health authorities should adopt and which should be rejected. In this sense, the question is not whether a surgery works, but whether *the decision to operate surgically* is a good policy or not, regardless of whether the patients all receive the operation or not. This view has parallels in studies of self-administered pharmaceuticals, where the interesting question from a health economic perspective is whether *prescription* of drug is cost-effective rather than the narrower *use* of drugs.

#### *7.1.2.3 Multidisciplinary rehabilitation: what is it?*

The effects of MDR on function and pain are described in the literature as strong to moderate, and no serious complications have been described [124, 125]. However, no consensus about a standard treatment regime exists, which makes it difficult to compare studies and choose a specific treatment. The MDR regimen used in this study has been shown to be acceptable as compared to fusion [124, 126]. The MDR procedure used in this study was described in articles published in 2003 and 2006 [106, 124]. and is referred to as the Brox regimen. An important element is the cognitive intervention. This includes exposing the patients to non-recommended activities and attempts to give the patient a new understanding of their problem. As described in chapter 4.2.3 on page 30, LBP has an important psychological element.

#### *7.1.2.4 Indirect costs*

Although the difference between the two groups was not statistically significant, there was an observed difference between the groups. This difference had big impact on the cost-effectiveness estimates. This is because the indirect costs were far higher than the direct costs. The difference in costs derived from the insignificant difference in return to work should thus be interpreted with caution.

#### *7.1.2.5 Limitations*

Looking at Figure 9 on page 49, it is apparent that at the end of the follow-up time, QoL is significantly different. It is thus safe to assume that longer follow-up time would show decidedly better cost-effectiveness for surgery than the baseline results indicate. A modelled analysis based on either data from other sources or longer follow-up within the same study would have permitted us to extend the follow-up period beyond 2 years and to include estimates of rare events. Also, with a modelling approach, other relevant treatment options (either a different kind of nonsurgical treatment or no treatment) could be compared with TDR.

### **7.1.3 Cost-Effectiveness of fusion in decompression surgery for Lumbar Spinal Stenosis (paper IV)**

This RCT revealed no clinical benefit 2 years after surgery of adding fusion surgery to decompression surgery. This was the case regardless of analyses methods and across different subgroup specifications. Approximately two thirds of the patients involved in the trial had a

follow-up longer than 5 years, and the lack of superiority of decompression plus fusion persists at 5 years among those patients. The more expensive surgery—with fusion—constitutes thus waste of health care resources.

*Table 10: Decompression and decompression + fusion. Data from Swespine yearly reports*

	<b>Decompression +fusion</b>	<b>Decompression</b>	<b>Fusion of all</b>
<b>2011</b>	835	1426	37%
<b>2012</b>	768	2717	22%
<b>2013</b>	790	2986	21%
<b>2014</b>	665	3217	17%
<b>2015</b>	NA	NA	12%
<b>2016</b>	NA	NA	9%

Of all surgeries in 2016 reported into Swespine database, 50% were for spinal stenosis. Of these, the vast majority were simple decompression surgeries or 87% and 7% decompression with fusion [127]. This was not always the case. In 2011, 37% of decompressions involved fusion. However, as the science began to evolve, and results from Swespine analyses started to emerge, for example in the 2013 paper of Försth et al. [128], this began to change, and in 2016, 9% included fusion. This has led to great savings of health care resources.

#### *7.1.3.1 Robust results*

In contrast to paper III, the results are robust across different assumptions. The results are valid only for patients who have spinal stenosis at one or two adjacent lumbar vertebral levels, with or without degenerative spondylolisthesis; this is the case for most patients with lumbar spinal stenosis and constitutes the most common indication for spine surgery. The per-protocol analysis and the modified intention-to-treat analysis (with only five patients who received an intervention missing from the analysis) revealed only minor differences between groups in overall results.

#### *7.1.3.2 Similar studies*

Several recent cohort studies have not shown any substantial benefit from the addition of fusion surgery to decompression surgery for lumbar spinal stenosis, even in the presence of spondylolisthesis [129–131]. A big analysis of the Swespine registry comes to the same conclusion [128].

However, the results of our trial might at first seem to contrast with the findings of Ghogawala et al. [132]. In their trial, the addition of fusion surgery to decompression surgery resulted in moderately superior scores on the SF-36 physical-component summary but not on the Oswestry disability index. However, the trial by Ghogawala et al. had a higher dropout rate and a substantially higher reoperation rate during follow-up in the decompression-alone group than in the fusion group (34% vs. 14%). This could have affected the results of the SF-36 assessment.

### *7.1.3.3 Fusion in addition to decompression is wasteful and potentially harmful*

The addition of fusion surgery to decompression surgery significantly increased direct hospital costs, including the costs of surgery and the in-hospital stay, but did not increase indirect costs at 2 years. Although economic data at 5 years were not collected, the clinical results and in particular the similar rates of reoperation in the two treatment groups indicate that the outcomes at 2 years are robust. As compared with decompression plus fusion, the use of decompression surgery alone not only is associated with a lower treatment cost per patient but also can save resources by releasing surgical capacity because of shorter operating time and hospitalization.

A large analysis of registry data showed that the addition of fusion surgery to decompression surgery doubled the risk of severe adverse events and was associated with an absolute risk difference that corresponded to a number needed to harm of 30 treated patients [133, 134]. Our trial was not powered to analyse differences in complication rates.

## **7.2 GENERAL DISCUSSION**

The elusive nature of low back pain (LBP), including lumbar disc herniation (LDH) and lumbar spinal stenosis (LSS) is one of the reasons why it is such a stubborn and costly disorder. The causes can be numerous. Diagnostics are very difficult. Indeed, many diagnoses are symptom-based as opposed to pathophysiological.

The available treatments are legion, ranging from no treatment, yoga and exercise to complex surgical procedures. The treatments' effectiveness is also often difficult to measure. As compared to the pharmaceutical industry where patents protect investments in expensive medical studies, the medical device industry has less incentive to study back pain and its treatments. In many cases, no treatment has been shown to be the best choice, but this can often be problematic for patients who prefer treatment to treat their debilitating pain to another round of wait-and-see with pain medication of differing efficacy. Therefore, the upwards trend of costs and burden do not show any signs of reversal.

The results from paper IV, which indicate the overuse of a more expensive and invasive treatment option for lumbar spinal stenosis, are a reminder that careful research, even on treatments that have been used for decades, has the potential of saving money without sacrificing treatment quality. Here, both register data and RCT's were used to arrive at similar conclusions. It is therefore good news that the proportion of fusions in connection with decompression, even in the presence of a degenerative slip, a spondylolisthesis, has been falling steadily in Sweden in the last decade.

Following the publication of this paper, multiple commentaries were published. Most were favourable to the study, its design and results. For example, in a commentary, Nancy Epstein asked: "With this clear message, why are so many spinal surgeons still offering fusions [...]?" Clearly, these fusions increase perioperative risks and complications resulting in longer LOS, even without considering the greater surgical/operative costs. How long will it take before

this clear message trickles down through the system and benefits the geriatric patients it presently hurts?” [135].

“Finally, when can we look forward to fewer morbidity/mortality conferences filled with these patients who are still undergoing unnecessarily extensive fusions resulting in a multitude of adverse events?” Epstein asked.

This thesis combines different methodologies and data sources. Prospective controlled studies have their pros and cons vis-à-vis retrospective register studies. Combining these two, for example by collecting data with the infrastructure of registries as done here, or by modelling where data from different sources are combined into a more complete whole, is an exciting way forward to combine the best of both worlds.

This also points to the more general issue of the value of health economic research. Mapping burden, and continually questioning the cost-effectiveness of various interventions is, in and of itself, a cost-effective endeavour. In relation with the total expenditure in the health care sector and the likelihood that current practices are inefficient, the cost of research is relatively low. However, this is not entirely unproblematic. As opposed to research in pharmaceuticals, orthopaedic research is impeded by infinite variations of techniques and approaches. Also, although such interventions are just as susceptible to the placebo effect, blinding through sham studies is problematic. Without careful randomisation and/or sophisticated statistics, bias is likely to show up, and confounders will pose a problem. However, using correct methods, several studies have reported that results achieved in observational studies are of equal significance as those from RCTs (see for example [11, 21, 136]).

Indeed, the part of the research team behind paper IV previously published a registry-based study using Swespine data. The study came to similar conclusions as the one presented here [128], stating that at two years, there was no significant difference in patient satisfaction between the two treatment groups for any of the outcome measures and that the proportion of patients who required subsequent further lumbar surgery was also similar in the two groups. The paper concludes that “In this large cohort the addition of fusion to decompression was not associated with an improved outcome.”

### **7.3 FUTURE RESEARCH**

Going through the papers specifically, papers I and II present interesting data set and model that could be explored further. Partly, this has already been done, in a paper examining the treatment patterns of patients following referral to specialist [137].

The model, presented in paper II, can be populated with data from different regions in Sweden, or from different countries, making it potentially a valuable tool for decision-making in structuring healthcare in regions or countries. Importantly, data from other contexts can be supplemented with the existing Swedish data or data from published sources where needed,

and still provide valuable insights into the burden and its different aspects in various countries. A potential expansion of the model is also to populate it with data from randomized controlled trials on the efficacy of different interventions.

Paper III, which as mentioned in chapter 0 was plagued by distorting horizon effect, should be revisited with longer-term data, either from the same population, from different population if possible, or as a fall-back option, with assumptions. The last exercise could reveal results according to different scenarios and as such be informative in its own albeit limited right.

Paper IV has huge potential impact and could be followed-up by detailing treatment patterns around the world and investigating whether and where low-value treatments are being used against current best evidence.

## 8 CONCLUSIONS

In paper I, we present cost estimates of the burden of low back pain in Sweden. The mean cost per LBP episode/patient was estimated at €2,761 and the total economic cost of all episodes that started in 2011 was estimated at €739 m (€78 per capita).

Most patients have a relatively benign course of the disorder, but a significant number experiences chronic symptoms. After onset of an LBP episode and different treatments, mean costs were not entirely restored to pre-episode levels during the two-year after the episode start, i.e. when the patient was first recorded in a health care register. This could be due to a continuous degenerative process that in fact has some persisting consequence to the patient, or a sign that the social and healthcare systems are not functioning optimally. The study gives no direct guidance of how resources should be allocated to improve efficiency but points at the importance of the consequences of LBP of different origin, both for the individual patients and the society.

Building on the data collected for paper I, paper II presents a novel economic model of lifetime treatment pathway based on both societal costs and quality-of-life in patients suffering from LBP of different origin. The large size of the underlying dataset, and the sophistication of the model, makes it, according to our knowledge, unique. The model shows that most patients with LBP receive conservative care, and a minority consume high-cost healthcare interventions like surgery.

Going into details on a specific treatment option for patients where their LBP is due to degenerated discs, the study finds that replacing the disc is potentially cost-effective in a short time perspective compared to the multidisciplinary alternative. The result was however not unequivocal and merits further research, particularly with longer follow-up.

Lastly, we find that in patients with lumbar spinal stenosis involving one or two adjacent vertebral levels, with or without degenerative spondylolisthesis, decompression with fusion did not result in clinical outcomes that were superior to those with decompression surgery alone. This indicates that a more invasive and expensive treatment has been used without merit for decades.

LBP of different origins is the most burdensome disease category in many Western societies. It is imperative to monitor how and where resources are spent and allocate them where they come of most use.

## 9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Ländryggssmärta har de senaste åren stigit till att ha den tyngsta sjukdomsbördan av alla sjukdomskategorier, enligt WHO:s mätningar. Detta är på grund av att ländryggssmärta är vanligt förekommande, är långvarig, ofta mycket smärtsam, kan påverka relativt unga människor och medför ofta stora kostnader, både inom sjukvårdssystemet och genom sin effekt på deltagande på arbetsmarknaden.

Ländryggssmärta är ett brett begrepp. Det innefattar oftast inte bara smärta i ländryggen, utan även i andra delar av kroppen, som till exempel i ben som kan bero på trängsel i ryggmärgskanalen, vilken i sin tur kan bero på ett diskbråck eller en spinal stenos (förträngning av ryggmärgskanalen). Smärtan är inte sällan muskulär, och kan bero på felaktig hållning och därav felaktig belastning på olika leder eller muskler. Diagnostik är ofta mycket svår. Olika behandlingsstrategier finns i stor mängd, och har varierande effekt.

Denna avhandling undersöker hälsoekonomiska aspekter av ländryggssmärta med eller utan utstrålning i benen, och består av fyra delarbeten. De två första använder sig av mycket stor databas som sammanställdes från olika nationella databaser och innehåller alla besök i Västra Götalandsregionen som inkluderar ryggsmärta under åren 2008–12. I den sammanställda databasen har vi även information om besök i sluten och öppen vård, sjukskrivningar, läkemedelsförskrivningar, kirurgiska operationer med mera.

I delarbete I analyserar vi den totala kostnaden i Sverige av ländryggssmärta kopplade till olika diagnoser och med eller utan bensmärta. Vi definierar en ryggepisod, som första dokumenterade besöket till en terapeut där ryggdiagnos anges som första ICD-kodade diagnos, och två år innan ett besök till ortopedspecialist, och sedan vidare till två år efter detta specialistbesök. Alla sjukvårdsbesök och kostnader ingår under denna fyra-års-period ingår. En episod anses avslutad om vi inte har hittat någon användning av sjukvårdens resurser på 6 månader. Vi kommer fram till att genomsnittsepisoden kostar €2 761 och att alla episoder som började år 2011 kostade €739 miljoner, eller €78 per capita.

De flesta patienterna förbättras spontant, utan större samhällskostnader. Dock fick en signifikant andel med kroniska besvär som leder till avsevärda kostnader. Snittkostnaden faller därför inte helt ner till det nivå den var två år innan episoden startade, vilket kan ses som ett tecken på att vi studerar en degenerativ åkomma. Studien ger inte direkta svar på hur behandling ska optimalt vara, men visar mönster och vikten av ländryggssmärta både för den enskilda patienten och samhället i stort.

Med hjälp av ovan beskrivna databas, beskriver delarbete II en ny hälsoekonomisk modell av livtidsbehandling av ländryggssmärta. Denna behandling är baserad på både kostnader och livskvalitetsmått. Storleken på databasen och detaljerna i modellen gör den unik i litteraturen. Modellen visar att de flesta patienterna får konservativ behandling och en minoritet konsumerar dyra ingrepp och behandlingar såsom kirurgi.

Delarbete III går mer i detalj. Där undersöks, i en randomiserad kontrollerad studie, om ett kirurgisk ingrepp för kronisk ländryggsmärta var kostnadseffektivt jämfört med icke-kirurgisk multidisciplinär behandling. Detta kunde inte bevisas.

I delarbete IV presenteras resultat från en annan randomiserad studie där patienter med förträngning i ryggradskanalen behandlades med antingen endast dekompression, ett kirurgiskt ingrepp där delar av kotbågen och benpålagringar tas bort, eller i kombination med en steloperation (fusion). Hälften av patienterna stelopererades i samband med dekompressionen, medan hälften fick endast en dekompression, som också kallas för nervfriläggning. Den förstnämnda kirurgin tar längre tid och är dyrare. Resultatet visar att tillägg av fusion inte förbättrade resultaten på vilket sätt det mättes. Detta betyder att denna dyrare version, dekompression plus fusion vid lumbal spinal stenosis, har utförts utan att det medför något värde för patienterna eller samhället.



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